Docket No.: 03108/0202223-US0
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Venkateswarlu Jasti et al.

Application No.: Not Yet Assigned

Confirmation No.: N/A

Filed: Concurrently Herewith

Art Unit: N/A

For: NOVEL TETRACYCLIC ARYLSULFONYL INDOLES HAVING SEROTONIN RECEPTOR AFFINITY USEFUL AS THERAPEUTIC AGENTS, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Examiner: Not Yet Assigned

AFFIRMATION OF PRIORITY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicant hereby claims priority under 35 U.S.C. 119 based on the following prior foreign application filed in the following foreign country on the date indicated:

Country	Application No.	Date
India	478/MAS/2002	June 21, 2002

A certified copy of the aforesaid Indian Patent Application was received by the International Bureau on August 14, 2003 during the pendency of International Application No. PCT/IN03/00222. A copy of Form PCT/IB/304 is enclosed.

Dated: December 20, 2004

Respectfully submitted,

By Sandra Lee

Sandra S. Lee
Registration No.: 51,932
(212) 527-7700
(212) 753-6237 (Fax)
Attorneys/Agents For Applicant

ECORD COPY

THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copies of Provisional & Complete Specification of the extract of Patent Application No. 478/MAS/2002 dated 21/06/2002 by M/s. Suven Pharmaceuticals Limited, Serene Chambers, an Indian Company of Road No.7, Banjara Hills, Hyderabad – 500 034, Andhra Pradesh, INDIA

.....

.....**In witness thereof**

I have hereunto set my hand

Dated this the 28th day of July 2003
6th day of Sravana, 1925 (Saka)

(K.M. VISWANATHAN)
ASSISTANT CONTROLLER OF PATENTS & DESIGNS

PATENT OFFICE BRANCH
GOVERNMENT OF INDIA
Guna Complex, 6th Floor, Annex.II
No.443, Anna Salai, Teynampet,
Chennai – 600 018

Form 2

THE PATENTS ACT, 1970

PROVISIONAL SPECIFICATION
(Section 10)

Novel tetracyclic arylsulfonyl indoles having serotonin receptor affinity useful as therapeutic agents, process for their preparation and pharmaceutical compositions containing them.

Suven Pharmaceuticals Limited, Serene Chambers, an Indian Company of Road No. 7, Banjara Hills, Hyderabad – 500 034, Andra Pradesh, India

The following specification particularly describes the nature of the invention:

Novel tetracyclic arylsulfonyl indoles having serotonin receptor affinity useful as therapeutic agents, process for their preparation and pharmaceutical compositions containing them

Field of Invention:

The present invention relates to substituted tetracyclic arylsulfonyl indole compounds, their derivatives, their analogues, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, and pharmaceutically acceptable compositions containing them. This invention particularly relates to novel tetracyclic arylsulfonyl indole, their derivatives, their analogues, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, and pharmaceutically acceptable compositions containing them. This invention also relates to the process for preparing such compounds, a composition containing such a compound and the use of such a compound and composition in medicine.

More particularly, the present invention relates to substituted tetracyclic arylsulfonyl indole compounds their derivatives, their analogues, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, and pharmaceutically acceptable compositions containing them and use of these compounds in medicine.

The present invention also relates to a process for the preparation of the above said novel compounds, their derivatives, their analogues, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates and pharmaceutical compositions containing them.

The compounds of - this invention are 5-HT ligands e.g. agonists or antagonists. Thus compounds of general formula (I) of this invention are useful for treating diseases wherein modulation of 5-HT activity is desired. Specifically, the compounds of this invention are useful in the treatment and / or prophylaxis of psychosis, paraphrenia, psychotic depression, mania, schizophrenia, schizophreniform disorders, anxiety, migraine headache, drug addiction, convulsive disorders, personality disorders, post-traumatic stress syndrome, alcoholism, panic attacks, obsessive-compulsive disorders and sleep disorders. The compounds of this invention are also useful in the treatment of psychotic, affective, vegetative and psychomotor symptoms of schizophrenia and the extrapyramidal motor side effects of other antipsychotic drugs.

The compounds of this invention are also useful in the treatment of neurodegenerative disorders like Alzheimer's disease, Parkinsonism and Huntington's chorea and chemotherapy-induced vomiting. The compounds of general formula (I) of this invention are also useful in modulation of eating behavior and thus are useful in treating excess weight and associated morbidity and mortality.

Background of the Invention

Many diseases of the central nervous system are influenced by the adrenergic, the dopaminergic, and the serotenergic neurotransmitter systems. Serotonin has been implicated in a number of diseases and conditions which originate in the central nervous system. These include diseases and conditions related to sleeping, eating, perceiving pain, controlling body temperature, controlling blood pressure, depression, anxiety, schizophrenia and other bodily states. (References: R.W. Fuller, Biology of Serotonergic Transmission, 221, 1982; D.J. Boullin, Serotonin in Mental abnormalities 1;316, 1978; J. Barchas et al., Serotonin and Behaviour, 1973. Serotonin also plays an important role in peripheral systems, such as the gastrointestinal system, where it has been found to mediate a variety of contractle, secretory and electrophysiologic effects.

Due to the broad distribution of serotonin within the body, there is lot of interest and use in drugs that affect serotonergic systems. In particular receptor specific agonists and antagonists are of interest for the treatment of a wide range of disorders, including anxiety, depression, hypertension, migraine, obesity, compulsive disorders, schizophernia, autism, neurodegenerative disorders like Alzheimer's disease, Parkinsonism and Huntington's chorea and chemotherapy-induced vomiting (Reference: M.D. Gershon et al, The peripheral actions of 5-Hydroxytryptamine, 246, 1989; P.R. Saxena et al, Journal of Cardiovascular Pharmacololgy, 15, supplement 7, 1990.

The major classes of serotonin receptors (5-HT_{1-7}) contain fourteen to eighteen separate receptors that have been formally classified (Reference: Glennon et al, Neuroscience and Behavioral Reviews, 1990, 14, 35 and D. Hoyer et al, Pharmacol Rev. 1994, 46, 157-203. Recently discovered information regarding subtype identity, distribution, structure and function suggests that it is possible to identify novel, subtype specific agents having improved therapeutic profiles with lesser side effects. The 5-HT6 receptor was identified in 1993 (Reference Monsma et al, Mol. Pharmacol, 1993, 43, 320-327 and Ruat M et al, Biochem. Biophys. Res. Com. 1993, 193, 269-276) Several antidepressants and atypical antipsychotics bind to the 5HT6 receptor with high affinity and this binding may be a factor in their profile of activities (Reference: Roth et al J. Pharm. Exp. Therapeu;t. 1994, 268, 1403-1410; Sleight et al, Exp. Opin. Ther. Patents 1998, 8, 1217-1224; Bourson et al, Brit. J.

Pharm. 1998, 125, 1562-1566; Boess et al, Mol. Pharmacol, 1998, 54, 577-583; Sleight et al, Brit. J. Pharmacol, 1998, 124, 556-562). In addition, the 5-HT6 receptor has been linked to generalized stress and anxiety states (Reference: Yoshioka et al, Life Sciences, 1998, 17/18, 1473-1477). Together these studies and observations suggest that compounds that antagonize the 5-HT6 receptor will be useful in treating disorders of the central nervous system.

U.S. Pat. No. 4,839,377, and U.S. Pat. No. 4,855,314, refer to 5-substituted 3-aminoalkyl indoles. The compounds are said to be useful for the treatment of migraine.

British Patent 2,035,310, refers to 3-aminoalkyl-1H-indole-5-thioamides and carboxamides. The compounds are said to be useful in treating hypertension, Raymond's disease and migraine.

European Patent Publication 303,506, refers to 3-poly:hydro-pyridyl-5-substituted-1H-indoles. The compounds are said to have 5-HT_1 receptor agonist and vasoconstrictor activity and to be useful in treating migraine.

European Patent Publication 354,777, refers to N-piperidinyl:indolyl:ethyl-alkane sulfonamide derivatives. The compounds are said to have 5-HT_1 receptor agonist and vasoconstrictor activity and to be useful in treating cephalic pain.

European Patent Publication 438,230, refers to indole-substituted five-membered heteroaromatic compounds. The compounds are said to have "5-HT_1-like" receptor agonist activity and to be useful in the treatment of migraine and other disorders for which a selective agonist of these receptors is indicated.

European Patent Publication 313,397, refers to 5-heterocyclic indole derivatives. The compounds are said to have exceptional properties for the treatment and prophylaxis of migraine, cluster headache, and headache associated with vascular disorders. These compounds are also said to have exceptional "5-HT_1-like" receptor agonism.

International Patent Publication WO 91/18897, refers to 5-heterocyclic indole derivatives. The compounds are said to have exceptional properties for the treatment and prophylaxis of migraine, cluster headache, and headache associated with vascular disorders. These compounds are also said to have exceptional "5-HT_1-like" receptor agonism.

European Patent Publication 457,701 refers to aryloxy amine derivatives as having high affinity for 5-HT_{1D} serotonin receptors. These compounds are said to be useful for treating diseases related to serotonin receptor dysfunction, for example, migraine.

European Patent Publication 497,512 A2, refers to a class of imidazole, triazole, and tetrazole derivatives which are selective agonists for "5-HT_1-like" receptors. These compounds are said to be useful for treating migraine and associated disorders.

International Patent Publication WO 93/00086, describes a series of tetrahydrocarbazole derivatives as 5-HT_1 receptor agonists useful for the treatment of migraine and related conditions.

International Patent Publications WO 93/23396, refers to fused imidazole and triazole derivatives as 5-HT_1 receptor agonists for the treatment of migraine and other disorders.

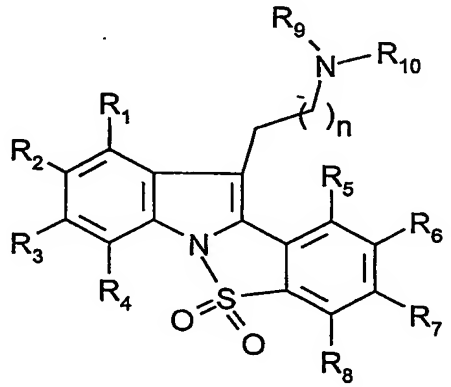
P. Schoeffter et al. refer to methyl 4-{4-[4-(1,1,3-trioxo-2H-1,2-benzoisothiazol-2-yl)butyl]-1-piperazinyl}1H-indole-3-carboxylate as a selective antagonist for the 5-HT_{1A} receptor in their paper "SDZ216-525, a selective and potent 5-Ht.sub.1A receptor antagonist" European Journal of Pharmacology, 244, 251-257 (1993).

International Patent Publication WO 94/06769, refers to 2-substituted-4-piperazine-benzothiophene derivatives that are serotonin 5-HT_{1A} and 5-HT_{1D} receptor agents useful in the treatment of anxiety, depression, migraine, stroke, angina and hypertension.

Summary of the Invention:

The present invention relates to substituted tetracyclic arylsulfonyl indole compounds their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, and pharmaceutically acceptable compositions containing them.

More particularly, the present invention relates to substituted tetracyclic arylsulfonyl indole compounds of the general formula (I),



General Formula (I)

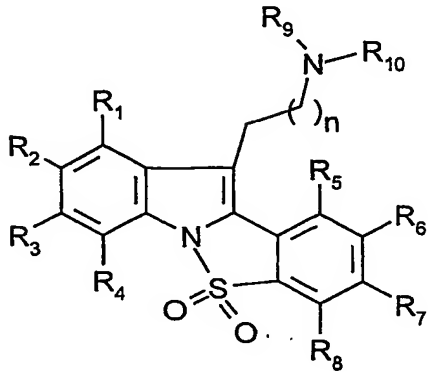
their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, and pharmaceutically acceptable compositions containing them and use of these compounds in medicine, wherein R_1,R_2, R_3, R_4, R_5, R_6, R_7 and R_8 may be same or different and represent hydrogen, halogen, perhaloalkyl, hydroxy, thio, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups selected from linear or branched (C_1-C_{12})alkyl, (C_2-C_{12})alkenyl, (C_2-C_{12})alkynyl (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkenyl, bicycloalkyl, bicycloalkenyl, (C_1-C_{12})alkoxy, cyclo(C_3-C_7)alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclyalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocycloalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl arylalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphonic acid and its derivatives; or the adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together with carbon atoms to which they are attached may form a five or a six membered ring, optionally containing one or more double bonds and optionally containing one or more heteroatoms selected from O, N, S and combinations of double bond and heteroatoms , "n" is an integer ranging from 1 to 8 and R_9 and R_{10} represents hydrogen, alkyl, aryl, aralkyl or together form a cyclic three to seven membered ring, optionally containing one or more double bonds and optionally containing one or more heteroatoms selected from "Oxygen", "Nitrogen", "Sulfur".

. It is preferred that n be 1 to 4. The carbon chains which "n" represents may be either linear or branched.

The present invention also relates to a process for the preparation of the above said novel compounds, their derivatives, their analogues, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates and pharmaceutical compositions containing them.

Detailed Description of the Invention:

The present invention relates to the compounds of the general formula (I)



General Formula (I)

wherein R_1,R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10} and "n" are as defined above.

Suitable groups represented by R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, may be selected from hydrogen, halogen atom such as fluorine, chlorine, bromine or iodine; perhaloalkyl particularly perhalo(C_1-C_6)alkyl such as fluoromethyl, difluoromethyl, trifluoromethyl, trifluoroethyl, fluoroethyl, difluoroethyl and the like; hydroxy, thio, amino, nitro, cyano, formyl, amidino, guanidino groups; substituted or unsubstituted (C_1-C_{12})alkyl group, especially, linear or branched (C_1-C_8)alkyl group, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-pentyl, iso-pentyl, hexyl, iso-hexyl, heptyl, octyl and the like; cyclo(C_3-C_7)alkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, the cycloalkyl group may be substituted; cyclo(C_3-C_7)alkenyl group such as cyclopentenyl, cyclohexenyl, cycloheptynyl, cycloheptadienyl, cycloheptatrienyl and the like, the cycloalkenyl group may be substituted; (C_1-C_{12})alkoxy, especially, (C_1-C_6)alkoxy group such as methoxy, ethoxy, propyloxy, butyloxy, iso-propyloxy and the like, which may be substituted; cyclo(C_3-C_7) alkoxy group such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and the like, the cycloalkoxy group may be substituted; aryl group such as phenyl or naphthyl, the aryl group may be substituted; aralkyl group such as benzyl, phenethyl, $C_6H_5CH_2CH_2CH_2$, naphthylmethyl and the like, the aralkyl group may be substituted and the substituted aralkyl is a group such as $CH_3C_6H_4CH_2$, Hal-$C_6H_4CH_2$, $CH_3OC_6H_4CH_2$, $CH_3OC_6H_4CH_2CH_2$ and the like; aralkoxy group such as benzyloxy, phenethyloxy, naphthylmethyloxy, phenylpropyloxy and the like, the aralkoxy group may be substituted; heterocyclyl groups such as aziridinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl and the like, the heterocyclyl group may be substituted; heteroaryl

group such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, imidazolyl, oxadiazolyl, tetrazolyl, benzopyranyl, benzofuranyl and the like, the heteroaryl group may be substituted; heterocyclo(C_1-C_6)alkyl, such as pyrrolidinealkyl, piperidinealkyl, morpholinealkyl, thiomorpholinealkyl, oxazolinealkyl and the like, the heterocyclo(C_1-C_6)alkyl group may be substituted; heteroaralkyl group such as furanmethyl, pyridinemethyl, oxazolemethyl, oxazolethyl and the like, the heteroaralkyl group may be substituted; heteroaryloxy, heteroaralkoxy, heterocycloalkoxy, wherein heteroaryl, heteroaralkyl, heterocycloalkyl and heterocyclylalkyl moieties are as defined earlier and may be substituted; acyl groups such as acetyl, propionyl or benzoyl, the acyl group may be substituted; acyloxy group such as CH_3COO, CH_3CH_2COO, C_6H_5COO and the like which may optionally be substituted, acylamino group such as CH_3CONH, CH_3CH_2CONH, C_3H_7CONH, C_6H_5CONH which may be substituted, (C_1-C_6)monoalkylamino group such as CH_3NH, C_2H_5NH, C_3H_7NH, $C_6H_{13}NH$ and the like, which may be substituted, (C_1-C_6)dialkylamino group such as $N(CH_3)_2$, $CH_3(C_2H_5)N$ and the like, which may be substituted; arylamino group such as C_6H_5NH, $CH_3(C_6H_5)N$, $C_6H_5(CH_3)NH$, NH-C_6H_4-Hal and the like, which may be substituted; arylalkylamino group such as $C_6H_5CH_2NH$, $C_6H_5CH_2CH_2NH$, $C_6H_5CH_2NCH_3$ and the like, which may be substituted; hydroxy(C_1-C_6)alkyl which may be substituted, amino(C_1-C_6)alkyl which may be substituted; mono(C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl group which may be substituted, alkoxyalkyl group such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like, which may be substituted; aryloxyalkyl group such as $C_6H_5OCH_2$, $C_6H_5OCH_2CH_2$, naphthyloxymethyl and the like, which may be substituted; aralkoxyalkyl group such as $C_6H_5CH_2OCH_2$, $C_6H_5CH_2OCH_2CH_2$ and the like, which may be substituted; (C_1-C_6)alkylthio, thio(C_1-C_6)alkyl which may be substituted, alkoxycarbonylamino group such s C_2H_5OCONH, CH_3OCONH and the like which may be substituted; aryloxycarbonylamino group as C_6H_5OCONH, $C_6H_5OCONCH_3$, $C_6H_5OCONC_2H_5$, $C_6H_4CH_3OCONH$, $C_6H_4(OCH_3)OCONH$ and the like which may be substituted; aralkoxycarbonylamino group such $C_6H_5CH_2OCONH$, $C_6H_5CH_2CH_2OCONH$, $C_6H_5CH_2OCON(CH_3)$, $C_6H_5CH_2OCON(C_2H_5)$, $C_6H_4CH_3CH_2OCONH$, $C_6H_4OCH_3CH_2OCONH$ and the like, which may be substituted; aminocarbonylamino group; (C_1-C_6)alkylaminocarbonylamino group, di(C_1-C_6)alkylaminocarbonylamino group; (C_1-C_6)alkylamidino group, (C_1-C_6)alkylguanidino, di(C_1-C_6)alkylguanidinogroups, hydrazino and hydroxylamino groups; carboxylic acid or its derivatives such as amides, like $CONH_2$, alkylaminocarbonyl like CH_3NHCO, $(CH_3)_2NCO$, C_2H_5NHCO, $(C_2H_5)_2NCO$, arylaminocarbonyl like PhNHCO, NapthNHCO and the like, aralkylaminocarbonyl such as $PhCH_2NHCO$, $PhCH_2CH_2NHCO$ and the like, heteroarylaminocarbonyl and

heteroaralkylamino carbo[redacted] groups where the heteroaryl groups[redacted] as defined earlier, heterocyclylaminocarbonyl where the heterocyclyl group is as defined earlier, carboxylic acid derivatives such as esters, wherein the ester moieties are alkoxycarbonyl groups such as unsubstituted or substituted phenoxycarbonyl, naphthyloxycarbonyl and the like; aralkoxycarbonyl group such as benzyloxycarbonyl, phenethyloxycarbonyl, naphthylmethoxycarbonyl and the like, heteroaryloxycarbonyl, heteroaralkoxycarbonyl, wherein the heteroaryl group is as defined earlier, heterocycloxycarbonyl where heterocycle is as defined earlier and these carboxylic acid derivatives may be substituted; sulfonic acid or its derivatives such as SO_2NH_2, SO_2NHCH_3, $SO_2N(CH_3)_2$, SO_2NHCF_3, $SO_2NHCO(C_1$-$C_6)$alkyl SO_2NHCOaryl where the aryl group is as defined earlier and the sulfonic acid derivatives may be substituted; phosphonic acid and its derivatives as $P(O)(OH)_2$, $P(O)(OC_1$-C_6-alkyl$)_2$, $P(O)$(O-aryl$)_2$ and the like.

Suitable cyclic structures formed by the two adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 orR_7 and R_8 together with the carbon atoms to which they are attached contain 5 to 6 ring atoms which may optionally contain one or moreheteroatoms selected from oxygen, nitrogen or sulfur and optionally contain one or more double bonds and optionally contain combination of double bond and hetero atoms as described earlier. the cyclic structures may be optionally substiuted phenyl, naphthyl, pyridyl, furanyl, thenyl, pyrrolyl, imidazolyl, pyrimidinyl, pyrazinyl and the like. suitable substituents on the cyclic structure formed by R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together with the adjacent carbon atoms to which they are attached include oxo, hydroxy, halogen atom such as chlorine, bromine and iodine; nitro, cyano, amino, formyl, $(c_1$-$c_3)$alkyl, $(c_1$-$c_3)$alkoxy, thioalkyl, alkylthio phenyl or benzyl groups.

R_9, R_{10} represents hydrogen, alkyl, aryl, aralkyl or together form a cyclic three to seven membered ring, optionally containing one or more double bonds and optionally containing one or more heteroatoms selected from "Oxygen", "Nitrogen", "Sulfur". The cyclic structures represent all the possibilities as described earlier and they may be substituted or unsubstituted. R_9, R_{10} preferably represents hydrogen, substituted or unsubstituted linear or branched $(C_1$-$C_{12})$alkyl like methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, pentyl, hexyl, octyl and the like; $(C_3$-$C_7)$cycloalkyl group, $(C_3$-$C_7)$cycloheteroalkyl with heteratoms like "Oxygen", "Nitrogen" and "Sulfur" . Suitable hetero cyclic rings formed by R_9 and R_{10} may be selected from pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolinyl, diazolinyl and the like.

The compounds of general formula (I) may have chiral centers and therefore may exist in different enantiomeric forms. This invention relates to all optical isomers and all stereoisomers and mixtures thereof.

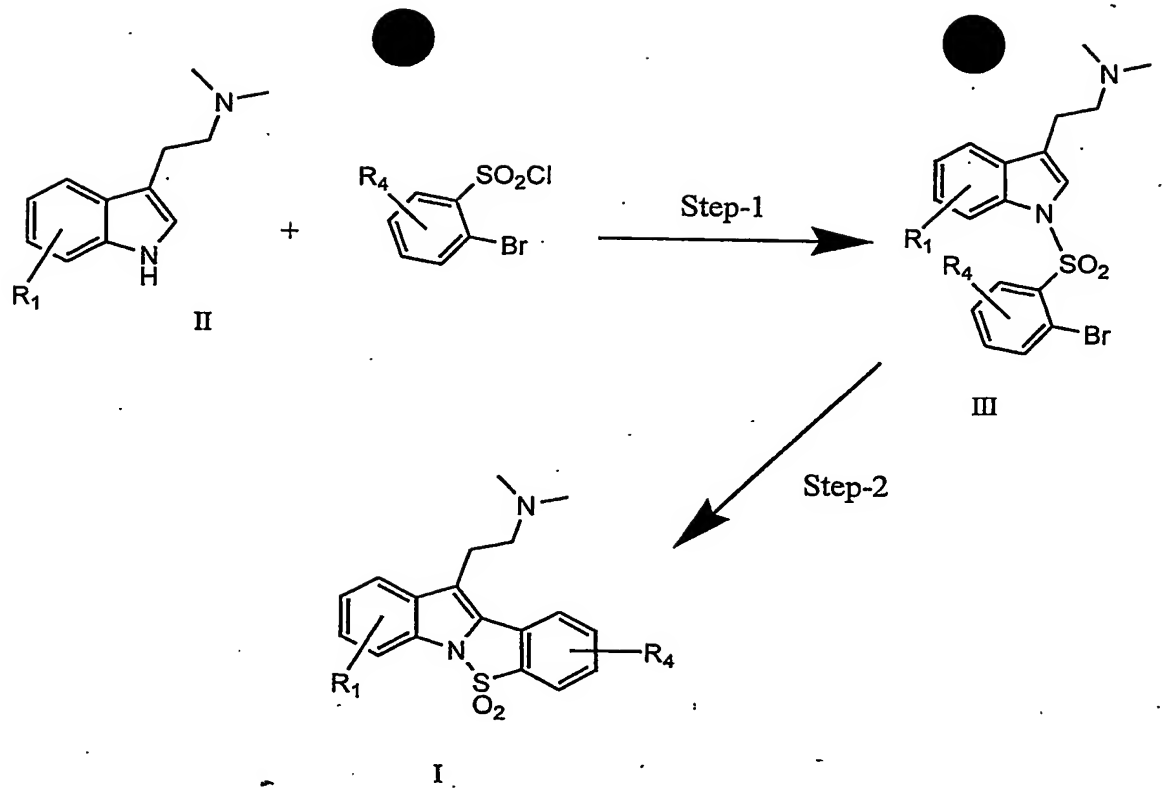
The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the general formula (I). The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benezenesulfonate, p-tolunesulfonate, palmoate and oxalate. Pharmaceutically acceptable salts forming part of this invention are intended to define but not limited to the above listed.

The present invention also relates to the pharmaceutically acceptable base salts of compound of general formula (I). The bases which are used to prepare the pharmaceutically acceptable base salts of the aforementioned acid compounds of this invention are those form non-toxic base salts i.e., salts containing pharmaceutically acceptable cations, such as Lithium, sodium, potassium, calcium and magnesium, salts of organic bases such as lysine, arginine, guanidine, diethonolamine, choline, tromethamine and the like; ammonium or substituted ammonium salts.

The present invention also relates to the process for the preparation of the above said novel compounds, their derivatives, their analogues, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10} and "n" are as defined previously can be prepared by any of the methods described below:

Compounds of general formula (I) are prepared by synthetic sequence shown in Scheme-I.

Scheme-I:



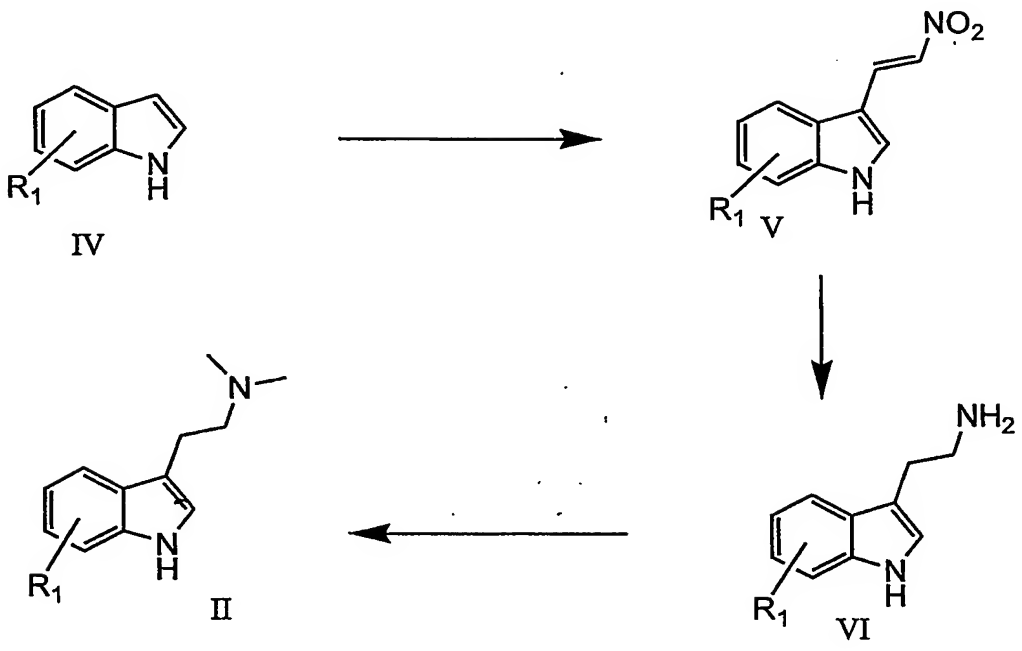
II III I

Step-1: Coupling of substituted N,N-dimethyl tryptamines (compounds of formula – II) with substituted 2-bromoarysulphonyl chloride produces compounds of formula – III. This reaction may be carried out in the presence of solvents such as THF, DMF, DMSO, DME, acetone and the like and preferably using either acetone or DMF. The inert atmosphere may be maintained by using inert gases such as N_2, Ar or He. The reaction may be affected in the presence of a base such as K_2CO_3, Na_2CO_3, NaH or mixtures thereof. The reaction temperature may range from 20 °C to 150 °C based on the choice of solvent and preferably at a temperature in the range from 30 °C to 100 °C. The duration of the reaction may range from 1 to 24 hours, preferably from 2 to 6 hours. (Reference: Bio Org. Med Chem. 2000. 10, 2295-2299).

Step-2: Cyclization of compounds of formula III using tetrakis Palladium catalyst yields the compounds of this invention of general formula (I). This cyclization reaction can be achieved using variety of triphenylphosphine palladium catalysts. The reaction may be affected in the presence of a base such as CH_3COOK. This reaction may be carried out in the presence of solvents such as THF, DMF, DMSO, DMA, DME, acetone and the like and preferably using Dimethylacetamide. The inert atmosphere may be maintained by using inert gases such as N_2, Ar or He. The reaction temperature may range from 50 °C to 200 °C based on the choice of solvent and preferably at a temperature of 160 °C. The duration of the reaction may range from 1 to 24 hours, preferably from 10 to 20 hours.

Compounds of formula – II (substituted N,N-dimethyl tryptamines) may be prepared by one of the following two routes.

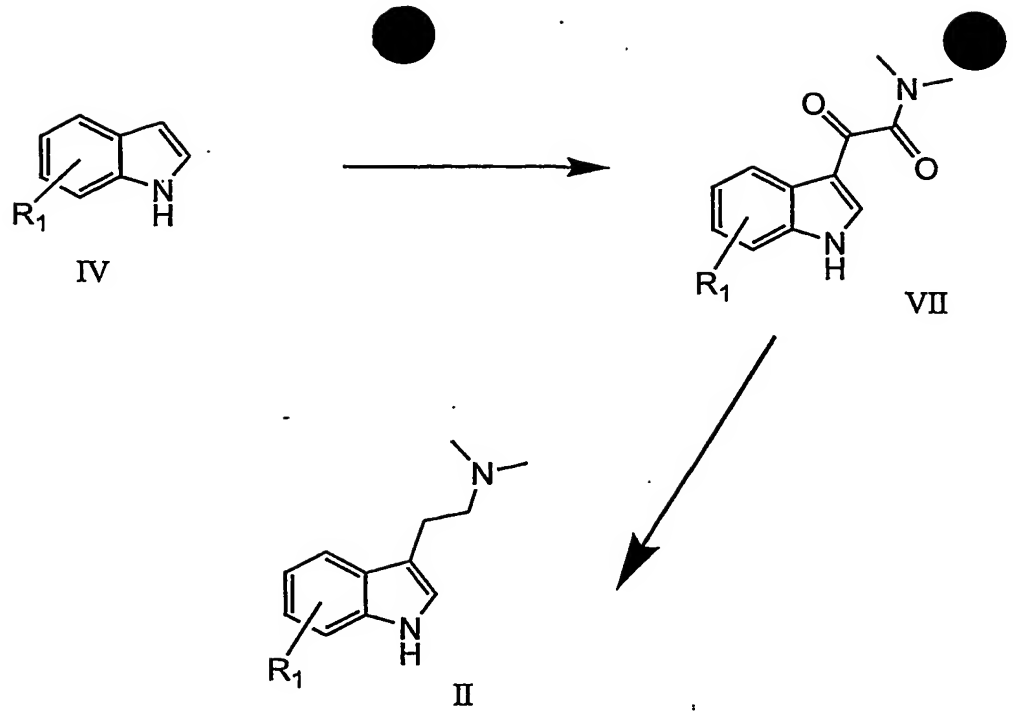
Route-1



Substituted indole compounds of formula (IV) can be alkylated with 1-dimethylamino-2-nitroethylene in the presence of trifluoroacetic acid to obtain compounds of formula (V). Compounds of formula (V) can be reduced with lithium aluminium hydride to give compounds of formula (VI) (substituted tryptamines). All steps are described in J. Med. Chem., 1993, 36, 4069 and J. Med Chem., 2000, 43, 1011-1018. The substituted tryptamine compounds of formula (VI) may be methylated through reductive alkylation using formaldehyde, sodium cyanoborohydride in acetonitrile stirring at room temperature for about 15 hours to produce N,N-dimethyl substituted tryptamines (compounds of formula II).

Alternatively compounds of formula II may be prepared by Route-2 also as described in the literature, J. Am Chem Soc., 1954, 76, 6208-6210, J. Chem Soc., 1965, 1424-1428 and J. Org. Chem, 1960, 25, 1542-1547.

Route-2:



Substituted indole compounds of formula (IV) are reacted with oxalyl chloride, followed by condensation with dimethylamine to produce compounds of formula (VII), followed by further reduction of compounds of formula (VII) using lithium alminium hydride to produce the N,N-dimethyl substituted tryptamines (compounds of formula II).

Substituted indole compounds (IV) may be prepared by the standard Fischer-indole synthesis.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed J.F. W. McOmie, Plenum Press, 1973; and T. W.Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The pharmaceutically acceptable salts forming a part of this invention may be prepared by treating the compound of formula (I) with 1-6 equivalents of a base such as sodium hydride, sodium methoxide, sodium ethoxide, sodium hydroxide, potassium t-butoxide, calcium hydroxide, calcium acetate, calcium chloride, magnesium hydroxide, magnesium chloride and the like. Solvents such as water, acetone, ether, THF, methanol, ethanol, t-butanol, dioxane, isopropanol, isopropyl ether or mixtures thereof may be used. Organic bases such lysine, arginine, methyl benzylamine, ethanolamine, diethanolamine,

tromethamine, choline, guanidine and their derivatives may be used. Acid addition salts, whereever applicable may be prepared by treatment with acids such as tartaric acid, mandelic acid, fumaric acid, maleic acid, lactic acid, salicyclic acid, citric acid, ascorbic acid, benzene sulfonic acid, p-toluene sulfonic acid, hydroxynaphthoic acid, methane sulfonic acid, malic acid, acetic acid, benzoic acid, succinic acid, palmitic acid, oxalic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and the like in solvents such as water, alcohols, ethers, ethyl acetate, dioxane, DMF or a lower alkyl ketone such as acetone, or mixtures thereof.

Different polymorphs may be prepared by crystallization of compounds of general formula (I) under different conditions such as different solvents or solvent mixtures in varying proportions for recrystallization, various ways of crystallization such as slow cooling, fast cooling or a very fast cooling or a gradual cooling during crystallization. Different polymorphs may also be obtained by heating the compound, melting the compound and solidification by gradual or fast cooling, heating or melting under vacuum or under inert atmosphere, and cooling under either vacuum or inert atmosphere. The various polymorphs may be identified by differential scanning calorimeter, powder X-ray diffraction, IR spectroscopy, solid probe NMR spectroscopy, thermal microsopy.

Another aspect of the present invention comprises a pharmaceutical composition, containing at least one of the compounds of the general formula (I), their derivatives, their analogs, their derivatives, their tautomeric forms, their steroisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates thereof as an active ingredient, together with pharmaceutically employed carriers diluents and the like.

The pharmaceutical compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention may be formulated for oral, buccal, intranasal, parenteral (e.g., intravenous, intramuscular or subcutaneous) or rectal administration or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or

suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters or ethyl alcohol); and preservatives (e.g., methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner.

The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the active compounds of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above is 0.1 to 200 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

Aerosol formulations for treatment of the conditions referred to above (e.g., migraine) in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains 20 .mu.g to 1000 .mu.g of the compound of the invention. The overall daily dose with an aerosol will be within the range 100 .mu.g to 10 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

The affinities of the compound of this invention for the various serotonin receptors are evaluated using standard radioligand binding assays as described in the literature.

The following examples illustrate the preparation of the compounds of the present invention. These are provided by the way of illustration only and therefore should not be construed to limit the scope of the invention. Commercial reagents were utilized without further purification. Melting points are uncorrected. NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent. Specific rotations were measured at room temperature using the sodium D (589 nm). Unless otherwise stated, all mass spectra were performed using ESI conditions. IR spectra were taken using KBr pellet. Room temperature refers to 25-30 °C. Chromatography refers to column chromatography performed using 60 – 120 mesh silica gel and executed under nitrogen pressure (flash chromatography) conditions.

A. General procedure for the preparation of substituted-3-(2-nitroethene-1-yl)indole :

To the previously cooled and stirred solution of trifluoroacetic acid maintained under N_2 atmosphere, was added 1-dimethylamino-2-nitroethylene in one portion. The solution was further cooled to 5 °C and substituted indole was added, maintaining the temperature at 5 °C. The reaction mixture was warmed to 25 to 30 °C and further stirred for 3 - 5 hrs. After the completion of reaction (tested by TLC), the mixture was poured on to 100 gm crushed ice and the product was extracted with ethyl acetate (2 x 30 mL). The organic layer was separated, washed with saturated sodium bicarbonate solution, followed by saturated sodium chloride solution and DM water and dried over sodium sulfate. Ethyl acetate was distilled off under reduced pressure to obtain the fine red colored solid, which was purified by column chromatography.

B. General procedure for the preparation of substituted tryptamines :

To the previously cooled and well stirred solution of lithium aluminum hydride in tetrahydrofuran, maintained at 0 °C under nitrogen atmosphere, was added a solution of substituted-3-(2-nitroethene-1-yl)indole in THF. After the complete addition, the reaction

mixture was refluxed for 1 - 2 hrs. After the completion of the reaction (tested by TLC), the reaction mixture was quenched with 100 gm cold water, followed by 100 mL of 15 % sodium hydroxide. The supernatant liquid was decanted and the residue was stirred with THF and filtered through Hyflow. The combined THF extracts were concentrated under vacuum to obtain a sticky solid, which was purified by column chromatography using silica gel using ethyl acetate and methanol in gradations.

C. General procedure for the preparation of substituted N,N-dimethyltryptamines:

Substituted tryptamine and formaldehyde was dissolved in acetonitrile and stirred at 25 - 28 °C. To this well stirred mixture, was added sodium cyanoborohydride, pH was adjusted to 4.5 - 5.5 with acetic acid and the reaction mixture was stirred overnight at 25 - 30 °C. After the completion of the reaction (tested by TLC), the reaction mixture was neutralized with 15 % sodium hydroxide solution and extracted with dichloromethane (2 x 30 mL). The combined dichloromethane extracts were washed with saturated solution of sodium carbonate, followed by brine and DM water and dried over sodium sulfate. Removal of dichloromethane by distillation afforded a sticky oil, which was purified by column chromatography using ethyl acetate and methanol as eluents.

D. General method for synthesis 2-bromoarylsulfonyl chlorides :

The 2-bromoaniline (0.2 mole) was taken into a four necked round bottomed flask, with water (60 mL) and the mixture was cooled with stirring. Conc. HCl (32 %, 60 mL) was added with stirring, which resulted in a clear solution, which was then cooled to - 5 °C. Aqueous sodium nitrite solution (16.6 gm, 0.24 moles in 20 mL water) was added slowly over 60 min. period to this above mixture, maintaining the temperature below 0 °C. The reaction mixture was further stirred for one hour at -5 to 0 °C. An aqueous SO_2 solution (10 % w/w) was cooled to -10 °C and added cupric chloride dihydrate (35 gm.) followed by potassium chloride (30 gm.). The above diazotised mixture was then slowly quenched into the latter solution maintaining the temperature below 5 °C. The reaction is further stirred at -5 °C for six hours, filtered the solids and washed with cold water. The solids were dissolved in toluene and filtered the un-dissolved mass. Organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residual mass was subjected to fractionation under reduced pressure to obtain the pure product.

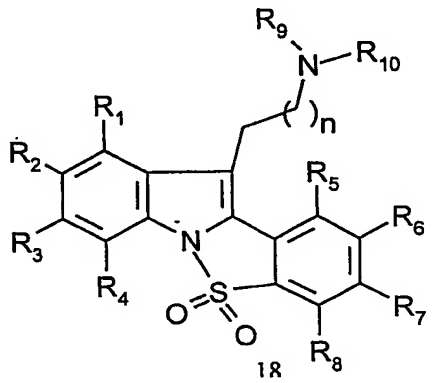
E. General procedure for the preparation of compounds of formula (III):

Sodium hydride (6.6 moles, 0.264 g., unwashed), and N,N-dimethyl-5-substituted-tryptamine (6.0 mmoles), was transferred to a 3 necked 50 mL round bottomed flask, maintained under nitrogen atmosphere. The reaction mixture was heated to 100 - 110 °C, till evolution of H_2 gas ceased. The reaction mixture was then cooled to 20 °C, 12 mL of dimethyl formamide was added and stirred well at 20 °C. A solution of 2-bromobenzenesulfonyl chloride in dimethyl formamide (6.0 mmoles, 1.7 g. in 7 mL of DMF) was then added to the above well stirred mixture, maintaining the reaction temperature below 20 °C (Exothermic reaction). The reaction mixture was maintained at 20 - 25 °C for further 20 hrs. After completion of reaction, the reaction mixture was quenched into 200 mL of saturated sodium bicarbonate solution with vigorous stirring and extracted with 2 x 50 mL of dichloromethane. Combined dichloromethane layer was washed with water, dried over sodium sulfate and evaporated under reduced pressure, below 50 °C. The crude residue was purified by silica gel column chromatography using 30 % methanol in ethyl acetate as a mobile phase, to obtain the intermediate, N,N-Dimethyl-1-(2'-bromophenylsulfonyl)-5-substituted tryptamine.

F. General procedure for the preparation of cyclized compounds of general formula (I):

1-(2'-bromophenylsulfonyl)-N,N-dimethyl-substituted tryptamine (0.286 moles) was taken in a 100 mL 3 necked round bottomed flask, along with N,N-dimethyl acetamide (40 mL), potassium acetate (0.286 moles, 0.281 g.) and dichloro bis(tri-o-tolylphosphine)palladium (0.0143 moles, 0.0126 g.). The reaction mixture was maintained under nitrogen atmosphere and was heated to 160 °C with stirring for 16 hrs. After the completion of reaction, excess of dimethyl acetamide was distilled off under reduced pressure and the residue was purified by silica gel column chromatography using 20 % methanol in ethyl acetate as an eluent. The final desired compound of general formula (I) can be further purified by preparation of their acid addition salts.

Representative examples of this invention of the general formula (I):



General formula (I)

The following compounds are purified and isolated as oxalate salts of general formula (I) as described above.

Compd. No	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9, R_{10}	n
1	H	H	H	H	H	H	H	H	CH_3	1
2	H	OCH_3	H	H	H	H	H	H	CH_3	1

Characterization data:

Compd. No.	M.P	IR (Cm^{-1})	NMR (δ)	MS
1	234-235 °C	3050; 1599; 1331; 1179; 748.	2.65(s, 6H, $N(CH_3)_2$); 2.92(m, 2H, CH_2); 3.23(m, 2H, CH_2); 7.0-7.9 (m, 9H, aromatic).	327$(M+H)^+$ 282.
2	237-239 °C	2959; 1592; 1318; 1235; 1178; 757; 796.	2.63(s, 6H, $N(CH_3)_2$); 2.96(m, 2H, CH_2); 3.23(m, 2H, CH_2); 3.87(s, 3H, $-OCH_3$); 6.9-7.9 (m, 8H, aromatic)	357$(M+H)^+$

Dated this the 20th day of June 2002-

H. SUBRAMANIAM
Of Subramaniam, Nataraj & Associates
Attorneys for the applicants

Abstract

The present invention relates to novel substituted tetracyclic arylsulfonyl indole compounds, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, and pharmaceutically acceptable compositions containing them. This invention particularly relates to novel tetracyclic arylsulfonyl indole compounds of the general formula (I), their derivatives, their analogues, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, and pharmaceutically acceptable compositions containing them and aprocess for the preparation thereof. This invention also relates to the process for preparing such compounds, a composition containing such a compound and the use of such a compound and composition in medicine. The compounds of general formula (I) of this invention are useful for treating diseases wherein modulation of 5-HT activity is desired. Specifically, the compounds of this invention are useful in the treatment and / or prophylaxis of psychosis, paraphrenia, psychotic depression, mania, schizophrenia, schizophreniform disorders, anxiety, migraine headache, drug addiction, convulsive disorders, personality disorders, post-traumatic stress syndrome, alcoholism, panic attacks, obsessive-compulsive disorders and sleep disorders. The compounds of this invention are also useful in the treatment of psychotic, affective, vegetative and psychomotor symptoms of schizophrenia and the extrapyramidal motor side effects of other antipsychotic drugs.

Form 2

THE PATENTS ACT, 1970

COMPLETE SPECIFICATION

(Section 10)

Novel tetracyclic arylsulfonyl indoles having serotonin receptor affinity useful as therapeutic agents, process for their preparation and pharmaceutical compositions containing them

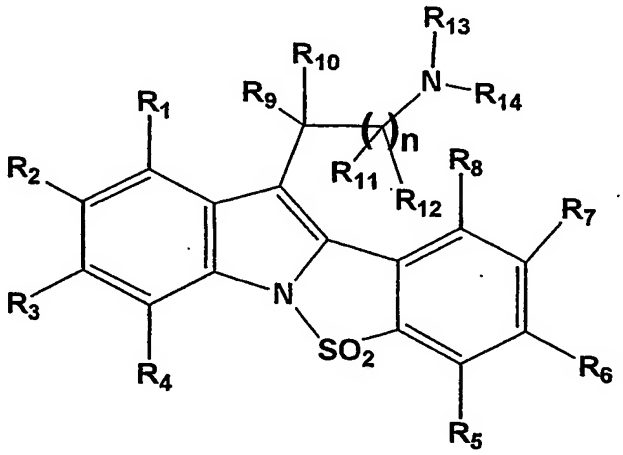
We, **SUVEN PHARMACEUTICALS LTD.**, an Indian company of Serene Chambers, Road No. 7, Banjara Hills, Hyderabad – 500 034, Andra Pradesh, India,

The following specification particularly describes and ascertains the nature of the invention and the manner in which it is to be performed:

Novel tetracyclic arylsulfonyl indoles having serotonin receptor affinity useful as therapeutic agents, process for their preparation and pharmaceutical compositions containing them

Field of Invention:

The present invention relates to novel tetracyclic arylsulfonyl indoles, their derivatives, their analogues, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates described herein and pharmaceutically acceptable compositions containing them.



General Formula (I)

The present invention also relates to the process for preparing the compounds of general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their geometric forms, their N-oxides, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates described herein and pharmaceutically acceptable compositions containing them.

The compounds of the general formula (I) of this invention are 5-HT (Serotonin) ligands e.g. agonists or antagonists. Thus, compounds of general formula (I) of this invention are useful for treating diseases wherein modulation of 5-HT (Serotonin) activity is desired. Specifically, the compounds of this invention are useful in the treatment and / or prophylaxis of psychosis, paraphrenia, psychotic depression, mania, schizophrenia, schizophreniform disorders, anxiety, migraine headache, depression, drug addiction, convulsive disorders, personality disorders, hypertension, autism, post-traumatic stress syndrome, alcoholism, panic attacks, obsessive-compulsive disorders and sleep disorders. T

The compounds of general formula (I) of this invention are also useful to treat psychotic, affective, vegetative and psychomotor symptoms of schizophrenia and the extrapyramidal motor side effects of other antipsychotic drugs.

The compounds of general formula (I) of this invention are also useful to treat neurodegenerative disorders like Alzheimer's disease, Parkinsonism and Huntington's chorea and chemotherapy-induced vomiting. The compounds of general formula (I) of this invention are also useful in modulation of eating behavior and thus are useful in reducing the morbidity and mortality associated with excess weight.

Background of the Invention

Many diseases of the central nervous system are influenced by the adrenergic, the dopaminergic and the serotenergic neurotransmitter systems. Serotonin has been implicated in a number of diseases and conditions, which originate in the central nervous system. these include diseases and conditions related to sleeping, eating, perceiving pain, controlling body temperature, controlling blood pressure, depression, anxiety, schizophrenia and other bodily states. (References: Fuller, R. W., Drugs Acting on Serotonergic Neuronal Systems, Biology of Serotonergic Transmission; John Wiley & Sons Ltd. (1982), 221-247; Boullin D. J., Serotonin in Mental abnormalities (1978), 1, 316; Barchas J. et. al., Serotonin and Behavior (1973)). Serotonin also plays an important role in the peripheral systems, such as the gastrointestinal system, where it has been found to mediate a variety of contractile, secretory and electrophysiologic effects.

Due to the broad distribution of serotonin within the body, there is lot of interest and use, in the drugs that affect serotonergic systems. Particularly, preferred are the compounds which have receptor specific agonism and/or antagonism for the treatment of a wide range of disorders, including anxiety, depression, hypertension, migraine, obesity, compulsive disorders, schizophrenia, autism, neurodegenerative disorders like Alzheimer's disease, Parkinsonism and Huntington's chorea and chemotherapy-induced vomiting (References: Gershon M. D. et. al., The peripheral actions of 5-Hydroxytryptamine (1989), 246; Saxena P. R. et. al., Journal of Cardiovascular Pharmacology (1990), supplement 7, 15).

The major classes of serotonin receptors (5-HT_{1-7}) contain fourteen to eighteen separate receptors that have been formally classified (References: Glennon et al, Neuroscience and Behavioral Reviews (1990), 14, 35 and Hoyer D. et al, Pharmacol. Rev. (1994), 46, 157-203). Recently discovered information regarding sub-type identity, distribution, structure and function suggests that it is possible to identify novel, sub-type specific agents having improved therapeutic profiles with lesser side effects. The 5-HT_6 receptor was identified in 1993 (References: Monsma et al, Mol. Pharmacol. (1993), 43, 320-327 and Ruat M. et al, Biochem. Biophys. Res. Com. (1993), 193, 269-276). Several antidepressants and atypical antipsychotics bind to the 5-HT_6 receptor with high affinity and this binding may be a factor in their profile of activities (References: Roth et al, J. Pharm. Exp. Therapeut. (1994), 268, 1403-1410; Sleight et al, Exp. Opin. Ther. Patents (1998), 8, 1217-1224; Bourson et al, Brit. J. Pharmacol. (1998), 125, 1562-1566; Boess et al, Mol.

Pharmacol., 1998, 54, 577-583; Sleight et al, Brit. J. Pharmacol. (1998), 124, 556-562). In addition, 5-HT_6 receptor has been linked to generalized stress and anxiety states (Reference: Yoshioka et al, Life Sciences (1998), 17/18, 1473-1477). Together these studies and observations suggest that compounds that antagonize the 5-HT_6 receptor will be useful in treating various disorders of the central nervous system.

U. S. Pat. No. 4,839,377 and U. S. Pat. No. 4,855,314 refer to 5-substituted 3-aminoalkyl indoles. The compounds are said to be useful for the treatment of migraine.

British Patent 2,035,310 refers to 3-aminoalkyl-1H-indole-5-thioamides and carboxamides. The compounds are said to be useful in treating hypertension, Raymond's disease and migraine.

European Patent Publication 303,506 refers to 3-polyhydropyridyl-5-substituted-1H-indoles. The compounds are said to have 5-HT_1 receptor agonists and vasoconstrictor activity and to be useful in treating migraine. European Patent Publication 354,777 refers to N-piperidinylindolylethyl-alkane sulfonamide derivatives. The compounds are said to be 5-HT_1 receptor agonists and have vasoconstrictor activity and are useful in treating cephalic pain.

European Patent Publication 438,230, refers to indole-substituted five-membered heteroaromatic compounds. The compounds are said to have "5-HT_1-like" receptor agonist activity and to be useful in the treatment of migraine and other disorders for which a selective agonist of these receptors is indicated.

European Patent Publication 313,397 refers to 5-heterocyclic indole derivatives. The compounds are said to have exceptional properties for the treatment and prophylaxis of migraine, cluster headache and headache associated with vascular disorders. These compounds are also said to have exceptional "5-HT_1-like" receptor agonism.

International Patent Publication WO 91/18897, refers to 5-heterocyclic indole derivatives. The compounds are said to have exceptional properties for the treatment and prophylaxis of migraine, cluster headache, and headache associated with vascular disorders. These compounds are also said to have exceptional "5-HT_1-like" receptor agonism.

European Patent Publication 457,701 refers to aryloxy amine derivatives as having high affinity for 5-HT_{1D} serotonin receptors. These compounds are said to be useful for treating diseases related to serotonin receptor dysfunction, for example, migraine.

European Patent Publication 497,512 A2, refers to a class of imidazole, triazole and tetrazole derivatives which are selective agonists for "5-HT_1-like" receptors. These compounds are said to be useful for treating migraine and associated disorders.

International Patent Publication WO 93/00086, describes a series of tetrahydrocarbazole derivatives, as 5-HT_1 receptor agonists, useful for the treatment of migraine and related conditions.

International Patent Publication WO 93/23396, refers to fused imidazole and triazole derivatives as 5-HT_1 receptor agonists, for the treatment of migraine and other disorders.

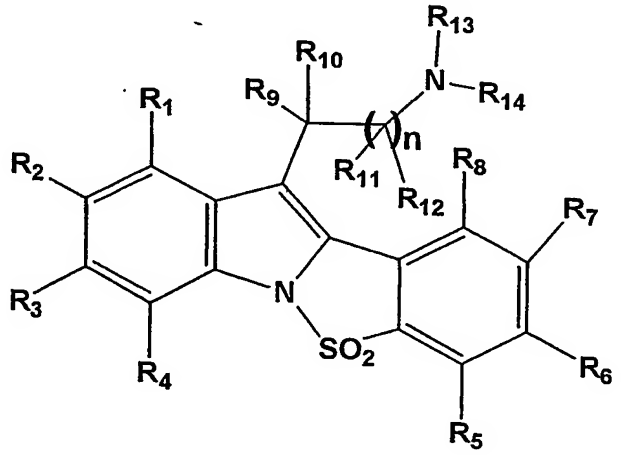
Schoeffter P. et al. refer to methyl 4-{4-[4-(1,1,3-trioxo-2H-1,2-benzoisothiazol-2-yl)butyl]-1-piperazinyl}1H-indole-3-carboxylate as a selective antagonist for the 5-HT_{1A} receptor in their paper "SDZ216-525, a selective and potent 5-HT_{1A} receptor antagonist" European Journal of Pharmacology, 244, 251-257 (1993).

International Patent Publication WO 94/06769, refers to 2-substituted-4-piperazine-benzothiophene derivatives that are serotonin 5-HT_{1A} and 5-HT_{1D} receptor agents useful in the treatment of anxiety, depression, migraine, stroke, angina and hypertension.

Summary of the Invention:

The present invention relates to novel tetracyclic arylsulfonyl indoles, their derivatives, their analogues, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates described herein and pharmaceutically acceptable compositions containing them.

More particularly, the present invention relates to novel tetracyclic arylsulfonyl indoles of the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates described herein and pharmaceutically acceptable compositions containing them and use of these compounds in medicine.



General Formula (I)

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups such as linear or branched (C_1-C_{12})alkyl, (C_2-C_{12})alkenyl, (C_2-C_{12})alkynyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkenyl, bicycloalkyl, bicycloalkenyl, (C_1-C_{12})alkoxy, cyclo(C_3-C_7)alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclylalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocyclylalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together with carbon atoms to which they are attached may form a 5, 6, or 7 membered ring, which may further optionally contain one or more double bonds and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and combinations of double bond and heteroatoms; or R_9 and R_{10} or R_{11} and R_{12} together represent double bond attached to "Oxygen" or "Sulfur"; or R_9 and R_{10} or R_{11} and R_{12} together with the carbon atoms to which they are attached may form a 3, 4, 5, or 6 membered ring, which may further optionally contain one or more double bonds, and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and also includes combination of one or more double bonds with "heteroatoms", as above defined.

R_{13} and R_{14} may be same or different and each independently represents hydrogen, substituted or unsubstituted groups such as linear or branched (C_1-C_{12})alkyl, (C_2-C_{12})alkenyl, (C_2-C_{12})alkynyl, (C_2-C_{12})alkanoyl (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkenyl, bicycloalkyl, bicycloalkenyl, aryl, aralkyl, heteroaryl, heterocyclylalkyl; optionally R_{13} and R_{14} along with the nitrogen atom, may form a 3, 4, 5, 6 or 7–membered heterocyclic ring, wherein the ring may be further substituted, and it may have either one, two or three double bonds or "additional heteroatoms", as defined above.

"n" is an integer ranging from 1 to 8. It is preferred that n be 1 to 4. The carbon chains which "n" represents may be either linear or branched.

Partial list of such compounds of general formula (I) is as follows:

6-(2-N,N-Dimethylaminoethyl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

4-Bromo-6-(2-N,N-dimethylaminoethyl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

4-Chloro-6-(2-N,N-dimethylaminoethyl)-benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-N,N-Dimethylaminoethyl)-4-fluorobenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-N,N-Dimethylaminoethyl)-4-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-N,N-Dimethylaminoethyl)-4-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide hydrochloride salt;
6-(2-N,N-Dimethylaminoethyl)-4-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide maleate salt;
6-(2-N,N-Dimethylaminoethyl)-4-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide D,L-malic acid salt;
6-(2-N,N-Dimethylaminoethyl)-4-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide oxalate salt;
6-(2-N,N-Dimethylaminoethyl)-4-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide citrate salt;
6-(2-N,N-Dimethylaminoethyl)-4-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-N,N-Dimethylaminoethyl)-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
4-Bromo-6-(2-N,N-dimethylaminoethyl)-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
4-Chloro-6-(2-N,N-dimethylaminoethyl)-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-N,N-Dimethylaminoethyl)-4-fluoro-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-N,N-Dimethylaminoethyl)-4-methyl-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-N,N-Dimethylaminoethyl)-4,8-dimethoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-N,N-Dimethylaminoethyl)-2-ethylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
2-Chloro-6-(2-N,N-dimethylaminoethyl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
2,4-Dichloro-6-(2-N,N-dimethylaminoethyl)-benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
2,3-Dichloro-6-(2-N,N-dimethylaminoethyl)-benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
5-Chloro-6-(2-N,N-dimethylaminoethyl)-2-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
2,4,5-Trichloro-6-(2-N,N-dimethylaminoethyl)-benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-N,N-Dimethylaminoethyl)-2,4-difluorobenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-N,N-dimethylaminoethyl)-4-fluoro-8-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
2,4-Difluoro-6-(2-N,N-dimethylaminoethyl)-8-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-N,N-Dimethylaminoethyl)-2-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-N,N-Dimethylaminoethyl)-2,8-dimethoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-N,N-Dimethylaminoethyl)-8-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

6-(3-N,N-Dimethylamino-1-hydroxyprop-1-yl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
4-Bromo-6-(3-N,N-Dimethylamino-1-hydroxyprop-1-yl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(3-N,N-Dimethylamino-1-hydroxyprop-1-yl)-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(3-N,N-Dimethylamino-1-hydroxyprop-1-yl)-8-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
4-Bromo-6-(3-N,N-dimethylamino-1-hydroxyprop-1-yl)-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-[2-(4-Methylpiperazin-1-yl)ethyl]benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-[2-Morpholin-4-ylethyl]benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-Pyrrolidin-1-ylethyl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-Piperidin-1-yl)ethyl]benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
4-Bromo-6-[2-morpholin-4-ylethyl]benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
4-Bromo-6-(2-pyrrolidin-1-ylethyl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
4-Bromo-6-[2-(4-methylpiperazin-1-yl)ethyl]benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(3-(Piperidin-1-yl)-1-hydroxyprop-1-yl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(3-(Piperidin-1-yl)-1-hydroxyprop-1-yl)-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
4-Bromo-6-(3-(piperidin-1-yl)-1-hydroxyprop-1-yl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
4-Bromo-6-(3-(piperidin-1-yl)-1-hydroxyprop-1-yl)-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(3-(Pyrrolidin-1-yl)-1-hydroxyprop-1-yl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(3-(Pyrrolidin-1-yl)-1-hydroxyprop-1-yl)-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-(N,N-Diethylamino)-2-methylethyl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-(N,N-Dimethylamino-1-hydroxy-1-yl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
4-Bromo-6-(2-(N,N-Dimethylamino-1-hydroxy-1-yl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-(N,N-Dimethylaminoethyl)-2,4-difluoro-8-Methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-(N,N-Dimethylamino-2-methylethyl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
4-Chloro-6-(2-(N,N-Dimethylaminoethyl)-8-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
8-(2-(N,N-Dimethylaminoethyl)benzo[d]isothiazolo[3,2-a]benzo(g)indol-S,S-dioxide; and
its stereoisomers, its N-oxides, its polymorphs, its pharmaceutically acceptable salts and solvates.

The present invention also envisages some useful bio-active metabolites of the compounds of general formula (I).

The compounds of general formula (I) of this invention are useful in the treatment and/ or prophylaxis of a condition wherein modulation of 5-HT activity is desired.

The present invention provides for use of the compounds of general formula (I) according to above, for the manufacture of the medicaments for the potential use in the treatment and/ or prophylaxis of certain CNS disorders such as, anxiety, depression, convulsive disorders, obsessive-compulsive disorders, migraine headache, cognitive memory disorders e.g. Alzheimer's disease and age-related cognitive decline, ADHD (Attention Deficient Disorder/ Hyperactivity Syndrome), personality disorders, psychosis, paraphrenia, psychotic depression, mania, schizophrenia, schizophreniform disorders, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, panic attacks, sleep disorders (including disturbances of Circadian rhythm) and also disorders associated with spinal trauma and / or head injury such as hydrocephalus. Compounds of the invention are further expected to be of use in the treatment of mild cognitive impairment and other neurodegenerative disorders like Alzheimer's disease, Parkinsonism and Huntington's chorea.

The compounds of the invention are also expected to be of use in the treatment of certain GI (Gastrointestinal) disorders such as IBS (Irritable bowel syndrome) or chemotherapy induced emesis.

The compounds of the invention are also expected to be of use in the modulation of eating behavior and these compounds can also be used to reduce morbidity and mortality associated with the excess weight.

The present invention provides a method for the treatment of a human or a animal subject suffering from certain CNS disorders such as, anxiety, depression, convulsive disorders, obsessive-compulsive disorders, migraine headache, cognitive memory disorders e.g. Alzheimer's disease and age-related cognitive decline, ADHD (Attention Deficient Hyperactivity Disorder), personality disorders, psychosis, paraphrenia, psychotic depression, mania, schizophrenia, schizophreniform disorders, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, panic attacks, sleep disorders (including disturbances of Circadian rhythm) and also disorders associated with spinal trauma and /or head injury such as hydrocephalus. Compounds of the invention are further expected to be of use in the treatment of mild cognitive impairment and other neurodegenerative disorders like Alzheimer's disease, Parkinsonism and Huntington's chorea.

The present invention also provides a method for modulating 5-HT receptor function desired in certain cases.

The present invention also includes a isotopically-labelled compounds, which are identical to those defined in the general formula (I), but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number found usually in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine, chlorine, iodine, bromine and mTecnitium, exemplified by ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{18}F, ^{99m}Tc, ^{31}P, S, ^{123}I and ^{125}I. Compounds of present invention and pharmaceutically acceptable salts and prodrugs of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention.

Isotopically labelled compounds of the present invention are useful in drug and/or substrate tissue distribution and target occupancy assays. For example, isotopically labelled compounds are particularly useful in SPECT (single photon emission computed tomography) and in PET (positron emission tomography)..

An effective amount of a compound of general formula (I) or its salt is used for producing medicaments of the present invention, along with conventional pharmaceutical auxiliaries, carriers and additives.

The present invention also relates to a pharmaceutical composition for treating and/or prophylaxis of disorders, a condition wherein modulation of 5-HT is desired in a mammal, preferably a human, comprising:

a. a pharmaceutically acceptable carrier

b. a compound of general formula (I) as defined above, and

c. a 5-HT re-uptake inhibitor, or its pharmaceutically acceptable salt;

wherein the amounts of each active compound (a compound of general formula (I) and a 5-HT re-uptake inhibitor), is such that the combination is effective in treating such a condition.

The present invention also relates to a method of treatment and/or prophylaxis of disorders, a condition wherein modulation of 5-HT is desired in a mammal, preferably a human, comprising:

a. a pharmaceutically acceptable carrier

b. a compound of general formula (I) as defined above, and

c. a 5-HT re-uptake inhibitor, or its pharmaceutically acceptable salt;

wherein the amounts of each active compound (a compound of general formula (I) and a 5-HT re-uptake inhibitor), is such that the combination is effective in treating such a condition.

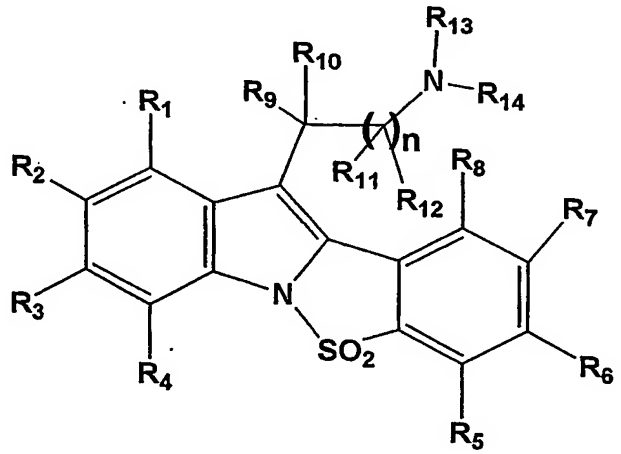
The present invention also relates to a process for the preparation of the above said novel compounds, their derivatives, their analogues, their tautomeric forms, their

stereoisomers, their geometric forms, their N-oxides, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates described herein and pharmaceutical compositions containing them.

Detailed description of the invention:

The present invention relates to novel tetracyclic arylsulfonyl indoles, their derivatives, their analogues, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates described herein and pharmaceutically acceptable compositions containing them.

More particularly, the present invention relates to novel tetracyclic arylsulfonyl indoles of the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates described herein and pharmaceutically acceptable compositions containing them and use of these compounds in medicine.



General formula (I)

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups such as linear or branched $(C_1\text{-}C_{12})$alkyl, $(C_2\text{-}C_{12})$alkenyl, $(C_2\text{-}C_{12})$alkynyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$cycloalkenyl, bicycloalkyl, bicycloalkenyl, $(C_1\text{-}C_{12})$alkoxy, cyclo$(C_3\text{-}C_7)$alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclylalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocyclylalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, aryloxyalkyl,

aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together with carbon atoms to which they are attached may form a 5, 6, or 7 membered ring, which may further optionally contain one or more double bonds and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and combinations of double bond and heteroatoms; or R_9 and R_{10} or R_{11} and R_{12} together represent double bond attached to "Oxygen" or "Sulfur"; or R_9 and R_{10} or R_{11} and R_{12} together with the carbon atoms to which they are attached may form a 3, 4, 5, or 6 membered ring, which may further optionally contain one or more double bonds, and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and also includes combination of one or more double bonds with "heteroatoms", as above defined.

R_{13} and R_{14} may be same or different and each independently represents hydrogen, substituted or unsubstituted groups such as linear or branched $(C_1\text{-}C_{12})$alkyl, $(C_2\text{-}C_{12})$alkenyl, $(C_2\text{-}C_{12})$alkynyl, $(C_2\text{-}C_{12})$alkanoyl $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$cycloalkenyl, bicycloalkyl, bicycloalkenyl, aryl, aralkyl, heteroaryl, heterocyclylalkyl; optionally R_{13} and R_{14} along with the nitrogen atom, may form a 3, 4, 5, 6 or 7–membered heterocyclic ring, wherein the ring may be further substituted, and it may have either one, two or three double bonds or "additional heteroatoms", as defined above.

"n" is an integer ranging from 1 to 8. It is preferred that n be 1 to 4. The carbon chains which "n" represents may be either linear or branched.

Suitable groups represented by R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} may be a halogen atom such as fluorine, chlorine, bromine or iodine; perhaloalkyl particularly perhalo$(C_1\text{-}C_6)$alkyl such as fluoromethyl, difluoromethyl, trifluoromethyl, trifluoroethyl, fluoroethyl, difluoroethyl and the like; substituted or unsubstituted $(C_1\text{-}C_{12})$alkyl group, linear or branched $(C_1\text{-}C_8)$alkyl group, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-pentyl, iso-pentyl, hexyl, iso-hexyl, heptyl, octyl and the like; substituted or unsubstituted $(C_2\text{-}C_{12})$alkenyl group such as ethylene, n-propylene pentenyl, hexenyl, heptynyl, heptadienyl and the like; $(C_2\text{-}C_{12})$alkynyl substituted or unsubstituted $(C_2\text{-}C_{12})$alkynyl group such as acetylene and the like; cyclo$(C_3\text{-}C_7)$alkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, the cycloalkyl group may be substituted; cyclo$(C_3\text{-}C_7)$alkenyl group such as cyclopentenyl, cyclohexenyl, cycloheptynyl, cycloheptadienyl, cycloheptatrienyl and the like, the cycloalkenyl group may be substituted; $(C_1\text{-}C_{12})$alkoxy, especially, $(C_1\text{-}C_6)$alkoxy group such as methoxy, ethoxy, propyloxy,

butyloxy, iso-propyloxy and the like, which may be substituted; cyclo(C_3-C_7) alkoxy group such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and the like, the cycloalkoxy group may be substituted; aryl group such as phenyl or naphthyl, the aryl group may be substituted; aralkyl group such as benzyl, phenethyl, $C_6H_5CH_2CH_2CH_2$, naphthylmethyl and the like, the aralkyl group may be substituted and the substituted aralkyl is a group such as $CH_3C_6H_4CH_2$, Hal-$C_6H_4CH_2$, $CH_3OC_6H_4CH_2$, $CH_3OC_6H_4CH_2CH_2$ and the like; aralkoxy group such as benzyloxy, phenethyloxy, naphthylmethyloxy, phenylpropyloxy and the like, the aralkoxy group may be substituted; heterocyclyl groups such as aziridinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl and the like, the heterocyclyl group may be substituted; heteroaryl group such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, imidazolyl, oxadiazolyl, tetrazolyl, benzopyranyl, benzofuranyl and the like, the heteroaryl group may be substituted; heterocyclo(C_1-C_6)alkyl, such as pyrrolidinylalkyl, piperidinylalkyl, morpholinylalkyl, thiomorpholinylalkyl, oxazolinylalkyl and the like, the heterocyclo(C_1-C_6)alkyl group may be substituted; heteroaralkyl group such as furanylmethyl, pyridinylmethyl, oxazolylmethyl, oxazolylethyl and the like, the heteroaralkyl group may be substituted; heteroaryloxy, heteroaralkoxy, heterocycloalkoxy, wherein heteroaryl, heteroaralkyl, heterocycloalkyl and heterocyclylalkyl moieties are as defined earlier and may be substituted; acyl groups such as acetyl, propionyl or benzoyl, the acyl group may be substituted; acyloxy group such as CH_3COO, CH_3CH_2COO, C_6H_5COO and the like which may optionally be substituted, acylamino group such as CH_3CONH, CH_3CH_2CONH, C_3H_7CONH, C_6H_5CONH which may be substituted, (C_1-C_6)monoalkylamino group such as CH_3NH, C_2H_5NH, C_3H_7NH, $C_6H_{13}NH$ and the like, which may be substituted, (C_1-C_6)dialkylamino group such as $N(CH_3)_2$, $CH_3(C_2H_5)N$ and the like, which may be substituted; arylamino group such as C_6H_5NH, $CH_3(C_6H_5)N$, $C_6H_4(CH_3)NH$, NH-C_6H_4-Hal and the like, which may be substituted; arylalkylamino group such as $C_6H_5CH_2NH$, $C_6H_5CH_2CH_2NH$, $C_6H_5CH_2NCH_3$ and the like, which may be substituted; hydroxy(C_1-C_6)alkyl which may be substituted, amino(C_1-C_6)alkyl which may be substituted; mono(C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl group which may be substituted, alkoxyalkyl group such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like, which may be substituted; aryloxyalkyl group such as $C_6H_5OCH_2$, $C_6H_5OCH_2CH_2$, naphthyloxymethyl and the like, which may be substituted; aralkoxyalkyl group such as $C_6H_5CH_2OCH_2$, $C_6H_5CH_2OCH_2CH_2$ and the like, which may be substituted; (C_1-C_6)alkylthio, thio(C_1-C_6)alkyl which may be substituted, alkoxycarbonylamino group such as C_2H_5OCONH, CH_3OCONH and the like which may be substituted; aryloxycarbonylamino group as C_6H_5OCONH, $C_6H_5OCONCH_3$, $C_6H_5OCONC_2H_5$, $C_6H_4CH_3OCONH$, $C_6H_4(OCH_3)OCONH$ and the like which may be substituted; aralkoxycarbonylamino group such $C_6H_5CH_2OCONH$, $C_6H_5CH_2CH_2OCONH$, $C_6H_5CH_2OCON(CH_3)$, $C_6H_5CH_2OCON(C_2H_5)$,

$C_6H_4CH_3CH_2OCONH$, $C_6H_4OCH_3CH_2OCONH$ and the like, which may be substituted; aminocarbonylamino group; (C_1-C_6)alkylaminocarbonylamino group, di(C_1-C_6)alkylaminocarbonylamino group; (C_1-C_6)alkylamidino group, (C_1-C_6)alkylguanidino, di(C_1-C_6)alkylguanidino groups, hydrazino and hydroxylamino groups; carboxylic acid or its derivatives such as amides, like $CONH_2$, alkylaminocarbonyl like CH_3NHCO, $(CH_3)_2NCO$, C_2H_5NHCO, $(C_2H_5)_2NCO$, arylaminocarbonyl like PhNHCO, NapthylNHCO and the like, aralkylaminocarbonyl such as $PhCH_2NHCO$, $PhCH_2CH_2NHCO$ and the like, heteroarylaminocarbonyl and heteroaralkylamino carbonyl groups where the heteroaryl groups are as defined earlier, heterocyclylaminocarbonyl where the heterocyclyl group is as defined earlier, carboxylic acid derivatives such as esters, wherein the ester moieties are alkoxycarbonyl groups such as unsubstituted or substituted phenoxycarbonyl, naphthyloxycarbonyl and the like; aralkoxycarbonyl group such as benzyloxycarbonyl, phenethyloxycarbonyl, naphthylmethoxycarbonyl and the like, heteroaryloxycarbonyl, heteroaralkoxycarbonyl, wherein the heteroaryl group is as defined earlier, heterocycloxycarbonyl where heterocycle is as defined earlier and these carboxylic acid derivatives may be substituted; sulfonic acid or its derivatives such as SO_2NH_2, SO_2NHCH_3, $SO_2N(CH_3)_2$, SO_2NHCF_3, $SO_2NHCO(C_1$-$C_6)$alkyl, SO_2NHCOaryl where the aryl group is as defined earlier and the sulfonic acid derivatives may be substituted; phosphoric acid and its derivatives such as $P(O)(OH)_2$, $P(O)(OC_1$-C_6-alkyl$)_2$, $P(O)$(O-aryl$)_2$ and the like.

Suitable cyclic structures formed by the two adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together with carbon atoms to which they are attached may form a five or a six membered ring, which may further optionally contain one or more double bonds and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" or a combination of one or more double bonds and hetero atoms. the cyclic structures may be optionally substituted phenyl, naphthyl, pyridyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrimidinyl, pyrazinyl and the like. Suitable substituents on the cyclic structure formed by R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together with the adjacent carbon atoms to which they are attached include oxo, hydroxy, halogen atom such as chlorine, bromine and iodine; nitro, cyano, amino, formyl, (C_1-C_3)alkyl, (C_1-C_3)alkoxy, thioalkyl, alkylthio phenyl or benzyl groups.

R_{13} and R_{14} represents hydrogen, substituted or unsubstituted linear or branched (C_1-C_{12})alkyl such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, pentyl, hexyl, octyl and the like; (C_2-C_{12})alkanoyl such as acetyl, propanoyl and the like; aryl group such as phenyl or naphthyl, the aryl group may be substituted; cyclo(C_3-C_7)alkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, the cycloalkyl group may be substituted; the aralkyl group may be substituted and the substituted aralkyl is a group such as $CH_3C_6H_4CH_2$, Hal-$C_6H_4CH_2$, $CH_3OC_6H_4CH_2$, $CH_3OC_6H_4CH_2CH_2$ and the like; (C_3-C_7)cycloheteroalkyl with

heteratoms like "Oxygen", "Nitrogen", "Sulfur" or "Selenium" optionally containing one or two, multiple bonds such as double or triple bonds. Suitable hetero cyclic rings formed between R_{13} and R_{14} along with "Nitrogen atom" be such as pyrrolyl, pyrrolidinyl, piperidinyl, pyridine, 1,2,3,4-Tetrahydro-pyridine, imidazolyl, pyrimidinyl, pyrazinyl, piperazinyl, diazolinyl and the like; the heterocyclyl group may be substituted; heteroaryl group such as pyridyl, imidazolyl, tetrazolyl and the like, the heteroaryl group may be substituted; heterocyclo(C_1-C_6)alkyl, such as pyrrolidinealkyl, piperidinealkyl, morpholinealkyl, thiomorpholinealkyl, oxazolinealkyl and the like, the heterocyclo(C_1-C_6)alkyl group may be substituted; heteroaralkyl group such as furanmethyl, pyridinemethyl, oxazolemethyl, oxazolethyl and the like, the heteroaralkyl group may be substituted; heteroaryloxy, heteroaralkoxy, heterocycloalkoxy, wherein heteroaryl, heteroaralkyl, heterocycloalkyl and heterocyclylalkyl moieties are as defined earlier and may be further substituted.

In the case of the compounds of general formula (I) having an asymmetric carbon atom the present invention relates to the D-form, the L-form and D,L- mixtures and in the case of a number of asymmetric carbon atoms, the diastereomeric forms and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. Those compounds of general formula (I) which have an asymmetric carbon and as a rule are obtained as racemates can be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. However, it is also possible to employ an optically active compound from the start, a correspondingly optically active or diastereomeric compound then being obtained as the final compound.

In the case of the compounds of general formula (I), where tautomerism may exist, the present invention relates to all of the possible tautomeric forms and the possible mixture thereof.

In the case of the compounds of general formula (I) containing geometric isomerism the present invention relates to all of these geometric isomers.

Suitable pharmaceutically acceptable acid addition salts of compounds of the general formula (I) can be prepared of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, includes, salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benezenesulfonate, p-tolunesulfonate, palmoate and oxalate.

Suitable pharmaceutically acceptable base addition salts of compounds of the general formula (I) can be prepared of the aforementioned acid compounds of this invention are those which form non-toxic base addition salts, includes, salts containing pharmaceutically acceptable cations, such as lithium, sodium, potassium, calcium and

magnesium, salts of organic bases such as lysine, arginine, guanidine, diethanolamine, choline, tromethamine and the like; ammonium or substituted ammonium salts.

Pharmaceutically acceptable salts forming part of this invention are intended to define but not limited to the above list.

In addition, pharmaceutically acceptable salts of the compound of formula (I) can be obtained by converting derivatives which have tertiary amino groups into the corresponding quarternary ammonium salts in the methods known in the literature by using quarternizing agents. Possible quarternizing agents are, for example, alkyl halides such as methyl iodide, ethyl bromide and n-propyl chloride, including arylalkyl halides such as benzyl chloride or 2-phenylethyl bromide.

In the addition to pharmaceutically acceptable salts, other salts are included in the invention. They may serve as intermediates in the purification of the compounds, in the preparation of other salts, or in the identification and characterization of the compounds or intermediates.

The pharmaceutically acceptable salts of compounds of formula (I) may exists as solvates, such as with water, methanol, ethanol, dimethylformamide, ethyl acetate, and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent preparation or crystallization, or adventitious to such solvent. Such solvates are within the scope of this invention.

The invention also encompasses the pharmaceutically acceptable prodrugs of the compounds of the formula (I). A prodrug is a drug which has been chemically modified and may be biologically in-active at the site of action, but which may be degraded or modified by one or more enzymatic or other in-vivo processes to the parent form. This prodrug should have a different pharmacokinetic profile than the parent, enabling easier absorption across the mucosal epithelium, better salt formation, or solubility, and/or improved systemic stability (an increase in the plasma half-life, for example). Typically, such chemical modifications include the following:

1. ester or amide derivatives which may be cleaved by esterases or lipases;
2. peptides which may be recognized by specific or non-specific proteases; or
3. derivatives that accumulate at a site of action through membrane selection of a prodrug from or a modified prodrug form; or any combination of 1 to 3, above.

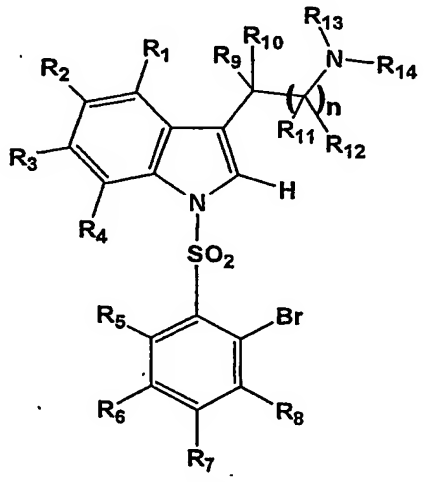
Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in H. Bundgard, Design of prodrugs, (1985).

Compounds of general formula (I) can be prepared by any of the methods described below. The present invention also provides processes for preparing compounds of general formula (I) as defined above, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their geometric forms, their polymorphs, their pharmaceutically acceptable

salts and their pharmaceutically acceptable solvates, novel intermediates described herein, where R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14} and "n" are as defined previously can be prepared by any of the methods described below:

Scheme - 1 :

Compounds of general formula **(I)**, may be prepared by cyclizing a novel intermediate of formula **(II)** given below,



(II)

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14} and "n" are as defined previously, using a Pd(0) or Pd (II) derivative as a catalyst, for example tetrakis triphenylphosphine palladium, (Bis-tri-o-tolylphosphine) palladium and the like; and thereafter if necessary:

i) converting a compound of the formula (I) into another compound of the formula (I); and/or

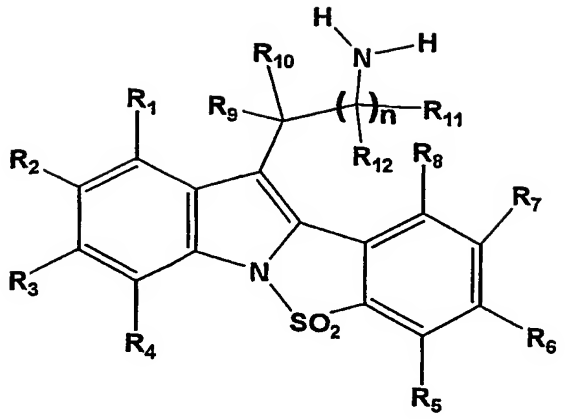
ii) removing any protecting groups; and/or

iii) forming a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof.

This cyclization reaction can be achieved using variety of Palladium catalysts. The reaction may be affected in the presence of a base such as CH_3COOK. This reaction may be carried out in the presence of solvents such as THF, DMF, DMSO, DMA, DME, acetone and the like and preferably using Dimethylacetamide. The inert atmosphere may be maintained by using inert gases such as N_2, Ar or He. The reaction temperature may range from 50 °C to 200 °C based on the choice of solvent and preferably at a temperature of 160 °C. The duration of the reaction may range from 1 to 24 hours, preferably from 10 to 20 hours.

Scheme - 2 :

Compounds of general formula **(I)**, may be prepared by reacting a compound of formula **(III)** given below,



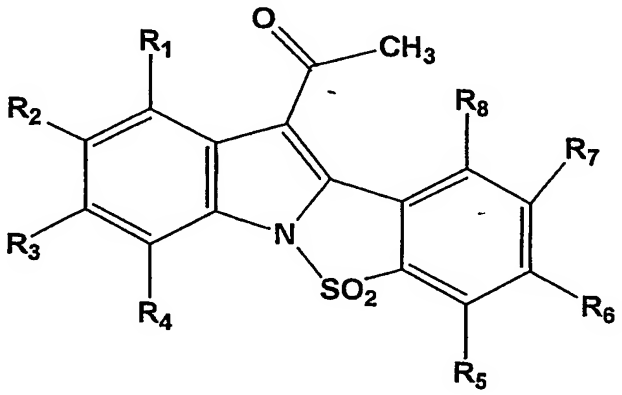
(III)

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12} and "n" are as defined previously, with a suitable alkylating agent such as $R_{13}X$ or $R_{14}X$ or $XR_{13}R_{14}X$ in successive steps or in one step, wherein X is good leaving group such as halogen, hydroxyl and the like.

The reaction is preferably carried in an organic solvent inert to the conditions of the reaction, such as acetone, THF or DMF and the like or mixtures thereof. The inert atmosphere may be maintained by using inert gases such as N_2, Ar or He. The reaction may be affected in the presence of a base such as K_2CO_3, Na_2CO_3, TEA or mixtures thereof. The reaction temperature may range from 20 °C to 200 °C based on the solvent employed and preferably at a temperature in the range from 30 °C to 150 °C. The duration of the reaction may range from 1 to 24 hours, preferably from 2 to 6 hours.

Scheme - 3 :

Compounds of general formula **(I)**, may be prepared by reacting a compound of formula **(IV)** given below,



(IV)

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and "n" are as defined previously, with formaldehyde and a compound of formula (V) given below,

$NHR_{13}R_{14}$

(V)

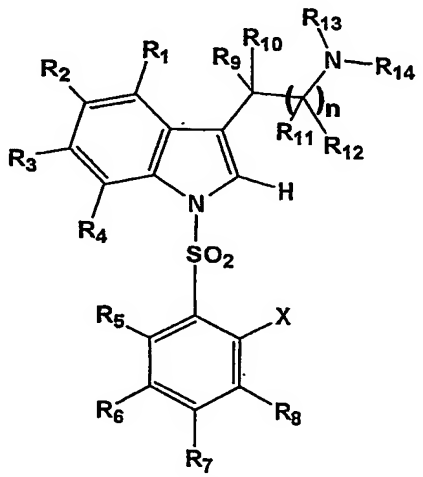
wherein R_{13} and R_{14} are as defined earlier.

The above reaction is preferably carried out at a temperature of 50 °C to 150 °C. The formaldehyde can be in the form of as aqueous solution i.e. 40 % formalin solution, or a polymeric form of formaldehyde such as paraformaldehyde or trioxymethylene. When such polymeric forms are used, a molar excess of mineral acid, for example hydrochloric acid, is added to regenerate the free aldehyde from the polymer. The reaction is preferably carried in an organic solvent inert to the conditions of the reaction, such as methanol, ethanol or 3-methylbutanol and the like or a mixture thereof, and preferably using either acetone or DMF. The inert atmosphere may be maintained by using inert gases such as N_2, Ar or He. The reaction temperature may range from 20 °C to 150 °C based on the choice of solvent and preferably at a temperature in the range from 30 °C to 100 °C. The duration of the reaction may range from 1 to 24 hours, preferably from 2 to 6 hours.

Scheme- 4 :

Compounds of general formula (I), may be prepared from another compound of formula (I) containing -C(=O) group/s in the side chain, by known methods of reduction to the corresponding –C(OH,H) or –C(H,H) compound.

Novel intermediates of general formula (II), their stereoisomers and their salts, represented as given below,



(II)

wherein X is halogen such chloro, bromo or iodo.

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups such as linear or branched $(C_1\text{-}C_{12})$alkyl, $(C_2\text{-}C_{12})$alkenyl, $(C_2\text{-}C_{12})$alkynyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$cycloalkenyl, bicycloalkyl, bicycloalkenyl, $(C_1\text{-}C_{12})$alkoxy, cyclo$(C_3\text{-}C_7)$alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy,

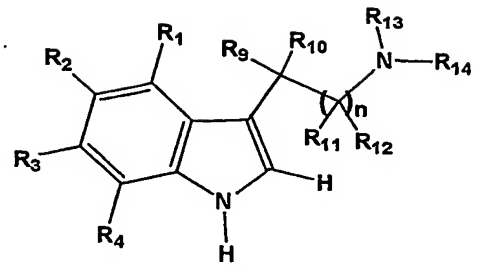
heteroaralkoxy, heterocyclylalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocyclylalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together with carbon atoms to which they are attached may form a 5, 6, or 7 membered ring, which may further optionally contain one or more double bonds and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and combinations of double bond and heteroatoms; or R_9 and R_{10} or R_{11} and R_{12} together represent double bond attached to "Oxygen" or "Sulfur"; or R_9 and R_{10} or R_{11} and R_{12} together with the carbon atoms to which they are attached may form a 3, 4, 5, or 6 membered ring, which may further optionally contain one or more double bonds, and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and also includes combination of one or more double bonds with "heteroatoms", as above defined.

R_{13} and R_{14} may be same or different and each independently represents hydrogen, substituted or unsubstituted groups such as linear or branched $(C_1\text{-}C_{12})$alkyl, $(C_2\text{-}C_{12})$alkenyl, $(C_2\text{-}C_{12})$alkynyl, $(C_2\text{-}C_{12})$alkanoyl $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$cycloalkenyl, bicycloalkyl, bicycloalkenyl, aryl, aralkyl, heteroaryl, heterocyclylalkyl; optionally R_{13} and R_{14} along with the nitrogen atom, may form a 3, 4, 5, 6 or 7–membered heterocyclic ring, wherein the ring may be further substituted, and it may have either one, two or three double bonds or "additional heteroatoms", as defined above.

"n" is an integer ranging from 1 to 8. It is preferred that n be 1 to 4. The carbon chains which "n" represents may be either linear or branched.

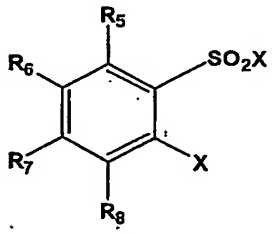
The present invention also provides processes for preparing the novel intermediate represented by the general formula **(II)**.

Route - 1 : Compounds of general formula **(II)**, may be prepared by reacting a compound of formula **(VI)** given below,



(VI)

where R_1, R_2, R_3, R_4, R_9, R_{10}, R_{11},R_{12}, R_{13} and R_{14} are as defined in relation to formula **(I)**; with a compound of formula **(VII)**



(VII)

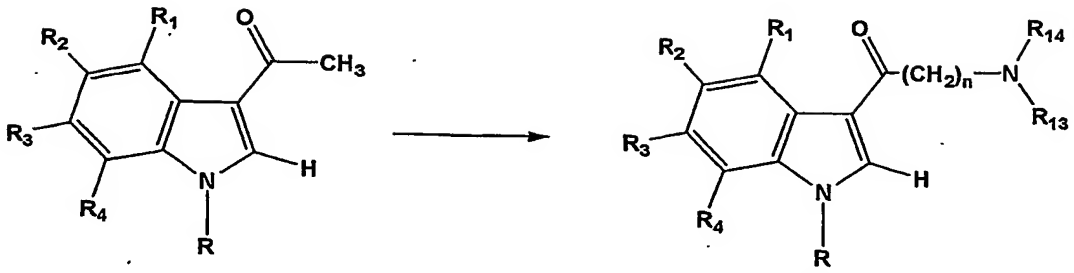
where R_5, R_6, R_7 and R_8 are as defined in relation to formula **(I)** and X is a halogen, preferably chloro, bromo or iodo.

This reaction may be carried out in the presence of solvents such as THF, DMF, DMSO, DME, acetone and the like and preferably using either acetone or DMF. The inert atmosphere may be maintained by using inert gases such as N_2, Ar or He. The reaction may be affected in the presence of a base such as K_2CO_3, Na_2CO_3, NaH, KH or mixtures thereof. The reaction temperature may range from 20 °C to 150 °C based on the choice of solvent and preferably at a temperature in the range from 30 °C to 100 °C. The duration of the reaction may range from 1 to 24 hours, preferably from 2 to 6 hours. (Reference: Bio Org. Med Chem. 2000. 10, 2295-2299).

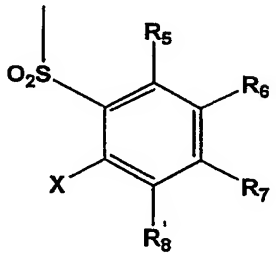
Preferably the substituents selected for the compounds of formula **(VI)** and **(VII)** are either not affected by the reaction conditions or else the sensitive groups are protected using suitable groups.

Compounds of formula **(VI)** are commercially available, or they may be prepared by conventional methods or by modification, using known processes, of commercially available compounds of formula **(VI)**. PCT patent application WO 02/078693 also provides methods to prepare variously substituted indoles as well as tryptamines and is incorporated herein by reference.

Route - 2 : Compounds of general formula (II) may be prepared by the following route



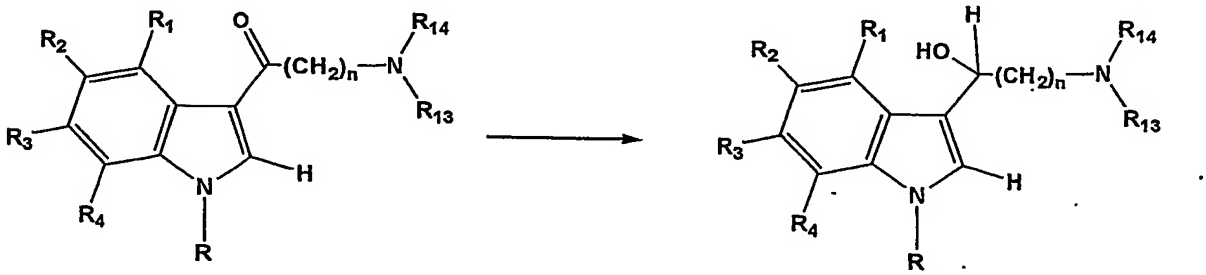
wherein R_1, R_2, R_3, R_4, R_{11}, R_{12}, R_{13}, R_{14} and n (=2) are as defined in relation to formula (I); R represents either of hydrogen or a group such as,



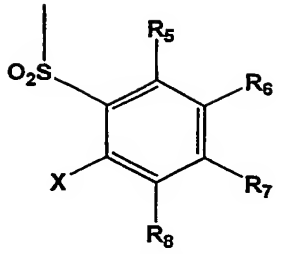
wherein X is halogen such as chloro, bromo or iodo; R_5, R_6, R_7 and R_8 are as defined earlier; in presence of amine hydrochloride and formaldehyde.

The above reaction is preferably carried out at a temperature of 50 °C to 150 °C. The formaldehyde can be in the form of as aqueous solution i.e. 40 % formalin solution, or a polymeric form of formaldehyde such as paraformaldehyde or trioxymethylene. When such polymeric forms are used, a molar excess of mineral acid, for example hydrochloric acid, is added to regenerate the free aldehyde from the polymer. The reaction is preferably carried in an organic solvent inert to the conditions of the reaction, such as methanol, ethanol or 3-methylbutanol and the like or a mixture thereof. The inert atmosphere may be maintained by using inert gases such as N_2, Ar or He. The reaction temperature may range from 20 °C to 150 °C based on the choice of solvent and preferably at a temperature in the range from 30 °C to 100 °C. The duration of the reaction may range from 1 to 24 hours, preferably from 2 to 6 hours.

Route - 3 : Compounds of general formula (II) may be prepared reducing another compound of formula (II) as follows,

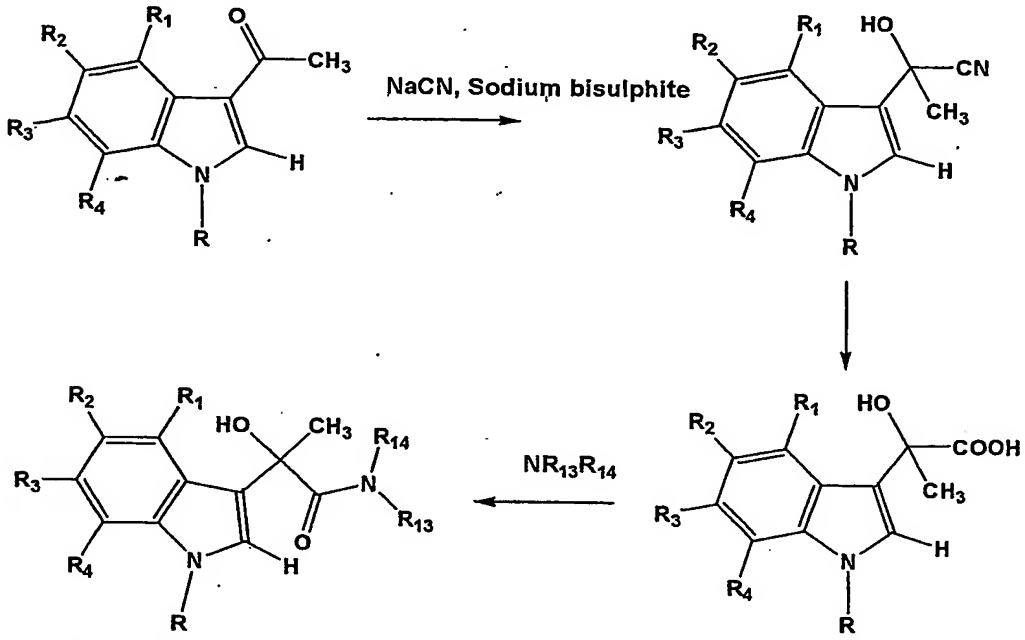


wherein R_1, R_2, R_3, R_4, R_{11}, R_{12}, R_{13}, R_{14} and n (=2) are as defined in relation to formula (I); R represents either of hydrogen or a group such as,

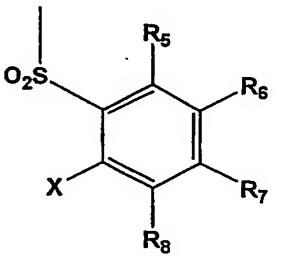


wherein X is halogen such as chloro, bromo or iodo; R_5, R_6, R_7 and R_8 are as defined earlier; by use of known various methods of either catalytic (for example, palladium/carbon), chemical (for example, sodium borohydride) or enzymatic reduction.

Route - 4 : Compounds of general formula (II) may be prepared by the following route



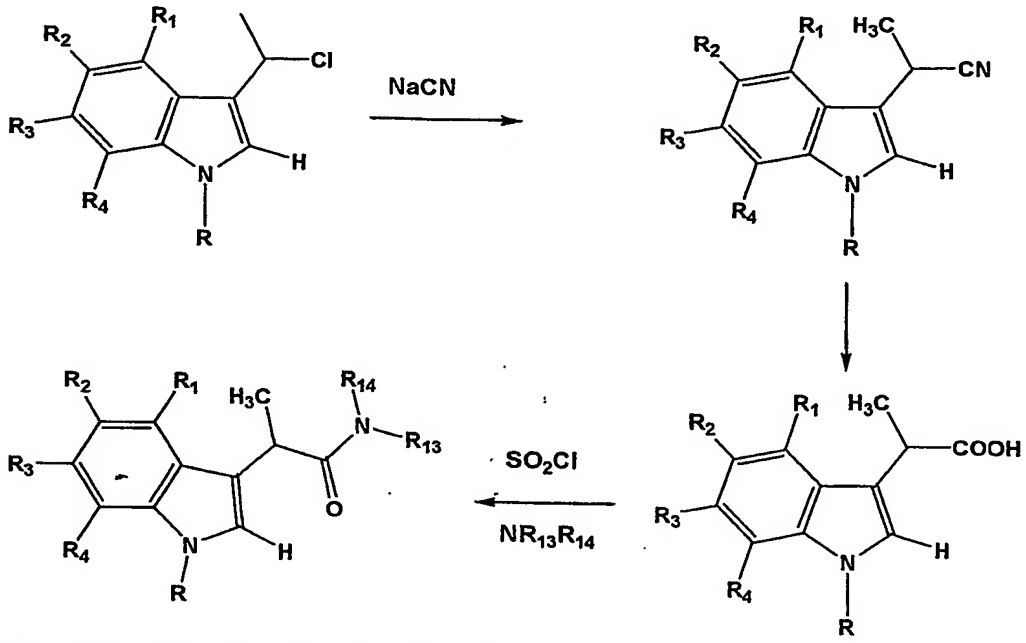
wherein R_1, R_2, R_3, R_4, R_{11}, R_{12}, R_{13}, R_{14} and n are as defined in relation to formula **(I)**; R represents either of hydrogen or a group such as,



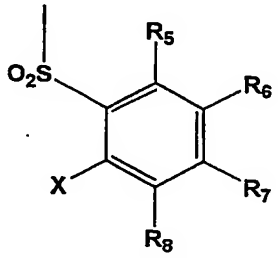
wherein X is halogen such as chloro, bromo or iodo; R_5, R_6, R_7 and R_8 are as defined earlier. The first step is well-known strecker reaction, which is followed by conversion of cyano to acid and lastly acid to amide.

The first step involves addition of aqueous solution of sodium bisulfite in the presence of sodium cyanide in a suitable aqueous solvent. The latter two conversions are very-well documented in the literature.

Route - 5 : Compounds of general formula (II) may be prepared by the following route

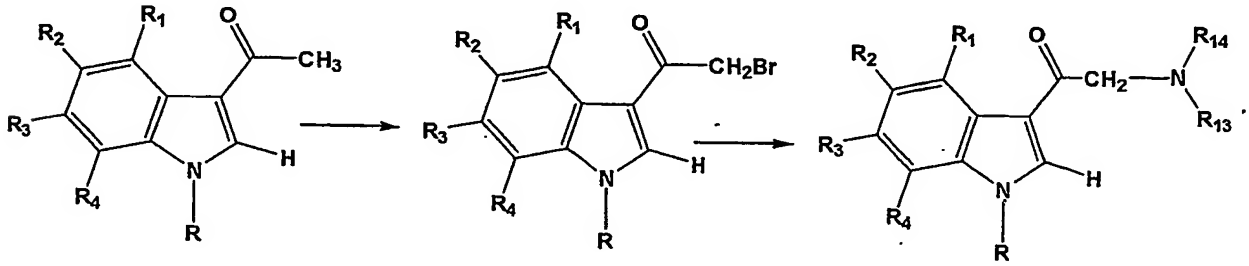


wherein R_1, R_2, R_3, R_4, R_{11}, R_{12}, R_{13}, R_{14} and n are as defined in relation to formula (I); R represents either of hydrogen or a group such as,

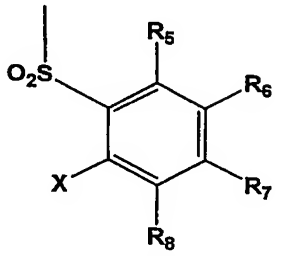


wherein X is halogen such as chloro, bromo or iodo; R_5, R_6, R_7 and R_8 are as defined earlier. The first step is well-known conversion of chloro to cyano, which is followed by conversion of cyano to acid and lastly acid to amide.

Route - 6 : Compounds of general formula (II) may be prepared by the following route,

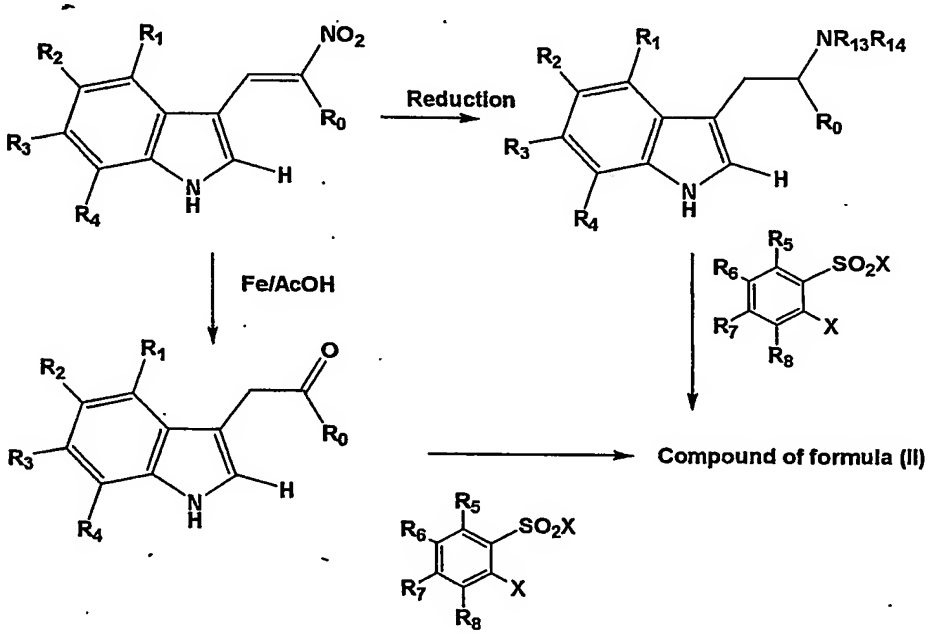


wherein R_1, R_2, R_3, R_4, R_{11}, R_{12}, R_{13}, R_{14} and n are as defined in relation to formula **(I)**; R represents either of hydrogen or a group such as,



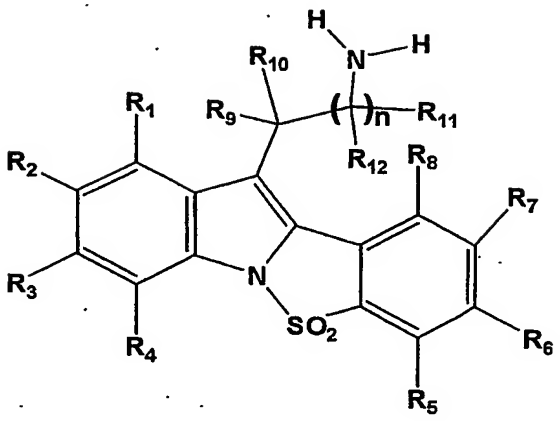
wherein X is halogen such as chloro, bromo or iodo; R_5, R_6, R_7 and R_8 are as defined earlier. The first step is bromination using suitable agent such as bromine, pyridinium-bromide and the like in a suiteble solvent. In the next step bromine is displaced by amine according to the methods known.

Route - 7 : Compounds of general formula (II) may be prepared by the following route,



wherein R_1, R_2, R_3, R_4, R_{11}, R_{12}, R_{13}, R_{14} and n (=2) are as defined in relation to formula **(I)**; R_0 is hydrogen or alkyl group. The starting material is well-known intermediate in indole chemistry, which upon oxidization leads to CH2-C(=O)- type substitution in the side chain. Next carrying out reaction sequence as described in Route 3 (i.e. reducing the carbonyl bond to hydroxyl) and Route 6 (i.e. bromination) differently substituted side chains can be prepared.

Novel intermediates of general formula **(III)** are represented as given below,

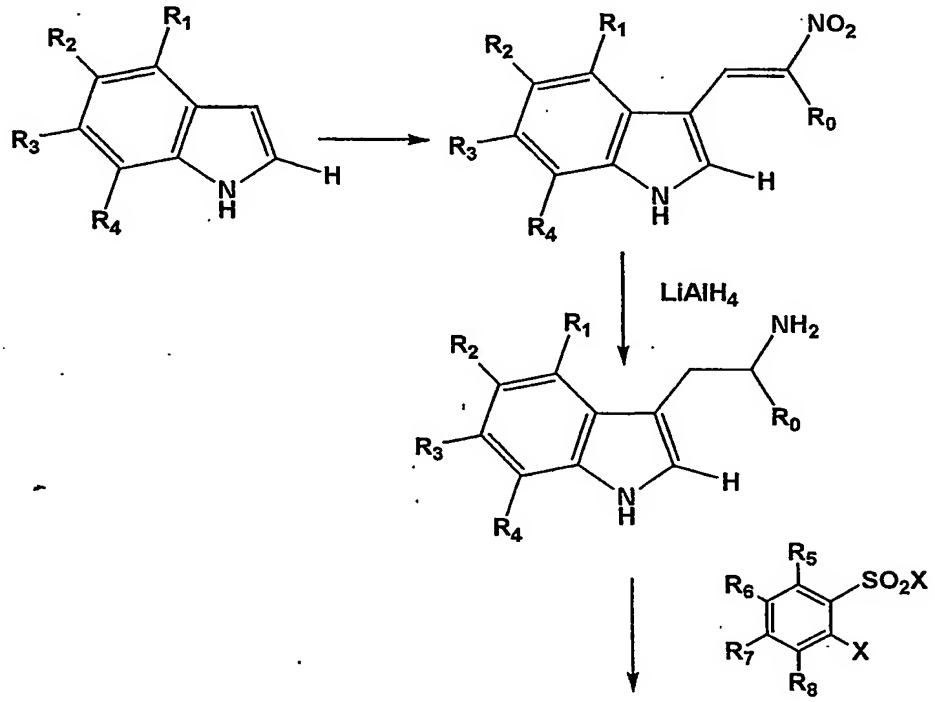


(III)

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups such as linear or branched $(C_1\text{-}C_{12})$alkyl, $(C_2\text{-}C_{12})$alkenyl, $(C_2\text{-}C_{12})$alkynyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$cycloalkenyl, bicycloalkyl, bicycloalkenyl, $(C_1\text{-}C_{12})$alkoxy, cyclo$(C_3\text{-}C_7)$alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclylalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocyclylalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together with carbon atoms to which they are attached may form a 5, 6, or 7 membered ring, which may further optionally contain one or more double bonds and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and combinations of double bond and heteroatoms; or R_9 and R_{10} or R_{11} and R_{12} together represent double bond attached to "Oxygen" or "Sulfur"; or R_9 and R_{10} or R_{11} and R_{12} together with the carbon atoms to which they are attached may form a 3, 4, 5, or 6 membered ring, which may further optionally contain one or more double bonds, and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and also includes combination of one or more double bonds with "heteroatoms", as above defined.

"n" is an integer ranging from 1 to 8. It is preferred that n be 1 to 4. The carbon chains which "n" represents may be either linear or branched.

The present invention also provides a process for preparing the novel intermediate represented by the general formula **(III)**.

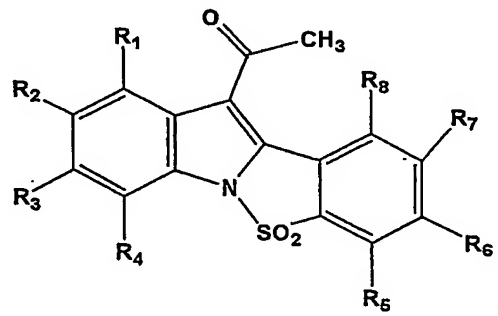


Compound of formula (III) ⟵ **Compound of formula (II)**

Substituted indole compounds can be alkylated with 1-dimethylamino-2-nitroethylene in the presence of trifluoroacetic acid, which can reduced with lithium aluminium hydride to give substituted tryptamines. All steps are described in J. Med. Chem., 1993, 36, 4069 and J. Med Chem., 2000, 43, 1011-1018.

The compounds of formula (II) can be methylated through reductive alkylation using formaldehyde, sodium cyanoborohydride in acetonitrile stirring at room temperature to produce compounds of formula (I).

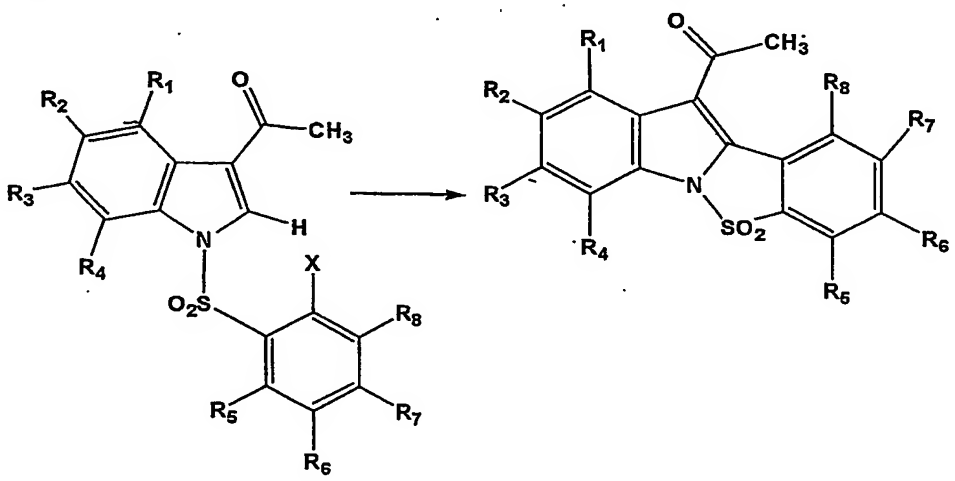
Novel intermediates of general formula **(IV)** are represented as given below,



(IV)

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7 and R_8 are as may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups such as linear or branched (C_1-C_{12})alkyl, (C_2-C_{12})alkenyl, (C_2-C_{12})alkynyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkenyl, bicycloalkyl, bicycloalkenyl, (C_1-C_{12})alkoxy, cyclo(C_3-C_7)alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclylalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocyclylalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together with carbon atoms to which they are attached may form a 5, 6, or 7 membered ring, which may further optionally contain one or more double bonds and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and combinations of double bond and heteroatoms; and R_9 and R_{10} here represent double bond attached to "Oxygen".

The present invention also provides method to prepare intermediate by general formula **(IV)**, which comprises of cyclizing compounds of formula **(VIII)**,



(VIII) **(IV)**

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7 and R_8 are as defined above; using a Pd(0) or Pd (II) derivative as a catalyst, for example tetrakis triphenylphosphine palladium, (Bis-tri-o-tolylphosphine) palladium and the like in a suitable solvent.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, Ed J. F. W. McOmie, Plenum Press, 1973; and T. W. Greene & P. G. M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. For example, suitable protecting groups for the piperazine group include BOC, $COCCl_3$, $COCF_3$. The protecting groups may be removed according to the standard procedures.

The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The compounds of the present invention may contain one or more asymmetric centers and therefore they also exist as stereoisomers. The stereoisomers of the compounds of the present invention may be prepared by one or more ways presented below:

i) One or more of the reagents may be used in their optically active form.

ii) Optically pure catalyst or chiral ligands along with metal catalyst may be employed in the reduction process. The metal catalyst may be Rhodium, Ruthenium, Indium and the like. The chiral ligands may preferably be chiral phosphines (Principles of Asymmetric synthesis, J. E. Baldwin Ed., Tetrahedron series, 14, 311-316).

iii) The mixture of stereoisomers may be resolved by conventional methods such as forming a diastereomeric salts with chiral acids or chiral amines, or chiral amino alcohols, chiral amino acids. The resulting mixture of diastereomers may then be separated by methods such as fractional crystallization, chromatography and the like, which is followed by an additional step of isolating the optically active product by hydrolyzing the derivative (Jacques et. al., "Enantiomers, Racemates and Resolution", Wiley Interscience, 1981).

iv) The mixture of stereoisomers may be resolved by conventional methods such as microbial resolution, resolving the diastereomeric salts formed with chiral acids or chiral bases.

Chiral acids that can be employed may be tartaric acid, mandelic acid, lactic acid, camphorsulfonic acid, amino acids and the like. Chiral bases that can be employed may be cinchona alkaloids, brucine or a basic amino acid such as lysine, arginine and the like.

The pharmaceutically acceptable salts forming a part of this invention may be prepared by treating the compound of formula (I) with 1-6 equivalents of a base such as Lithium, ammonia, substituted ammonia, sodium hydride, sodium methoxide, sodium ethoxide, sodium hydroxide, potassium t-butoxide, calcium hydroxide, calcium acetate, calcium chloride, magnesium hydroxide, magnesium chloride and the like. Solvents such as

water, acetone, ether, THF, methanol, ethanol, t-butanol, dioxane, isopropanol, isopropyl ether or mixtures thereof may be used. Organic bases such lysine, arginine, methyl benzylamine, ethanolamine, diethanolamine, tromethamine, choline, guanidine and their derivatives may be used. Acid addition salts, wherever applicable may be prepared by treatment with acids such as tartaric acid, mandelic acid, fumaric acid, maleic acid, lactic acid, salicyclic acid, citric acid, ascorbic acid, benzene sulfonic acid, p-toluene sulfonic acid, hydroxynaphthoic acid, methane sulfonic acid, malic acid, acetic acid, benzoic acid, succinic acid, palmitic acid, oxalic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and the like in solvents such as water, alcohols, ethers, ethyl acetate, dioxane, DMF or a lower alkyl ketone such as acetone, or the mixtures thereof.

Different polymorphs may be prepared by crystallization of compounds of general formula (I) under different conditions such as different solvents or solvent mixtures in varying proportions for recrystallization, various ways of crystallization such as slow cooling, fast cooling or a very fast cooling or a gradual cooling during crystallization. Different polymorphs may also be obtained by heating the compound, melting the compound and solidification by gradual or fast cooling, heating or melting under vacuum or under inert atmosphere and cooling under either vacuum or inert atmosphere. The various polymorphs may be identified by either one or more of the following techniques such as differential scanning calorimeter, powder X-ray diffraction, IR spectroscopy, solid probe NMR spectroscopy and thermal microscopy.

Another aspect of the present invention comprises of a pharmaceutical composition, containing at least one of the compounds of the general formula (I), their derivatives, their analogs, their derivatives, their tautomeric forms, their stereoisomers, their geometric forms, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates thereof as an active ingredient, together with pharmaceutically employed carriers, auxiliaries and the like.

The pharmaceutical compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention may be formulated for oral, buccal, intranasal, parental (e.g., intravenous, intramuscular or subcutaneous) or rectal administration or a form suitable for administration by inhalation or insufflation.

The dose of the active compounds can vary depending on factors such as the route of administration, age and weight of patient, nature and severity of the disease to be treated and similar factors. Therefore, any reference herein to a pharmacologically effective amount of the compounds of general formula (I) refers to the aforementioned factors.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically

acceptable excipients such as binding agents (e.g., pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters or ethyl alcohol); and preservatives (e.g., methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner.

The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of an aerosol spray from a pressurized container or a nebulizer, or from a capsule using a inhaler or insufflator. In the case of a pressurized aerosol, a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas and the dosage unit may be determined by providing a valve to deliver a metered amount. The medicament for pressurized container or nebulizer may contain a solution or suspension of the active compound while for a capsule it preferably should be in the form of powder. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the active compounds of this invention, for either oral, parenteral, nasal or buccal administration, to an average adult human, for the treatment of the conditions referred to above, is 0.1 to 200 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

Aerosol formulations for treatment of the conditions referred to above (e.g., migraine) in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains 20 μg to 1000 μg of the compound of the invention. The overall daily dose with an aerosol will be within the range 100 μg to 10 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

The affinities of the compound of this invention for the various serotonin receptors are evaluated using standard radioligand binding assays and are described here.

Radioligand binding assays for various 5-HT receptor sub-types :

i) Assay for $5HT_{1A}$

Materials and Methods:

Receptor source : Human recombinant expressed in HEK-293 cells

Radioligand : [3H]-8-OH-DPAT (221 Ci/mmol)

Final ligand concentration - [0.5 nM]

Reference compound : 8-OH-DPAT

Positive control : 8-OH-DPAT

Incubation conditions :

Reactions are carried out in 50 mM TRIS-HCl (pH 7.4) containing 10 mM $MgSO_4$, 0.5 mM EDTA and 0.1% Ascorbic acid at room temperature for 1 hour. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound with the $5HT_{1A}$ binding site.

Literature Reference:

- Hoyer D., Engel G., et al. Molecular Pharmacology of $5HT_1$ and $5\text{-}HT_2$ Recognition Sites in Rat and Pig Brain Membranes: Radioligand Binding Studies with [^{3}H]-5HT, [^{3}H]-8-OH-DPAT, [^{125}I]-Iodocyanopindolol, [^{3}H]-Mesulergine and [^{3}H]-Ketanserin. Eur. Jrnl. Pharmacol. 118: 13-23 (1985) with modifications.
- Schoeffter P. and Hoyer D. How Selective is GR 43175? Interactions with Functional $5\text{-}HT_{1A}$, $5HT_{1B}$, $5\text{-}HT_{1C}$, and $5\text{-}HT_{1D}$ Receptors. Naunyn-Schmiedeberg's Arch. Pharmac. 340: 135-138 (1989) with modifications.

ii) Assay for $5HT_{1B}$

Materials and Methods:

Receptor source : Rat striatal membranes

Radioligand : [^{125}I]Iodocyanopindolol (2200 Ci/mmol)

Final ligand concentration - [0.15 nM]

Non-specific determinant : Serotonin - [10 μM]

Reference compound : Serotonin

Positive control : Serotonin

Incubation conditions :

Reactions are carried out in 50 mM TRIS-HCl (pH 7.4) containing 60 μM (-) isoproterenol at 37^{0}C for 60 minutes. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound with the 5HT$_{1B}$ binding site.

Literature Reference:

- Hoyer D., Engel G., et al. Molecular Pharmacology of 5HT$_1$ and 5-HT$_2$ Recognition Sites in Rat and Pig Brain Membranes: Radioligand Binding Studies with [^{3}H]-5HT, [^{3}H]-8-OH-DPAT, [^{125}I]-Iodocyanopindolol, [^{3}H]-Mesulergine and [^{3}H]-Ketanserin. *Eur. Jml. Pharmacol.* 118: 13-23 (1985) with modifications.
- Schoeffter P. and Hoyer D. How selective is GR 43175? Interactions with Functional 5-HT$_{1A}$, 5HT$_{1B}$, 5-HT$_{1C}$, and 5-HT$_1$ Receptors. *Naunyn-Schmiedeberg's Arch. Pharmac.* 340: 135-138 (1989) with modifications.

iii) Assay for 5HT$_{1D}$

Materials and Methods:

Receptor source : Human cortex

Radioligand : [^{3}H] 5-Carboxamidotryptamine (20-70 Ci/mmol)

Final ligand concentration - [2.0 nM]

Non-specific determinant : 5-Carboxamidotryptamine (5-CT) - [1.0 μM]

Reference compound : 5-Carboxamidotryptamine (5-CT)

Positive control : 5-Carboxamidotryptamine (5-CT)

Incubation conditions :

Reactions are carried out in 50 mM TRIS-HCl (pH 7.7) containing 4 mM $CaCl_2$, 100 nM 8-OH-DPAT, 100 nM Mesulergine, 10 uM Pargyline and 0.1% ascorbic acid at 25 °C for 60 minutes. The reaction is terminated by rapid vacuum filtration onto glass fiber filters.

Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound with the cloned $5HT_{1D}$ binding site.

Literature Reference:

- Waeber C., Schoeffter, Palacios J.M. and Hoyer D. Molecular Pharmacology of the 5-HT_{1D} Recognition Sites: Radioligand Binding Studies in Human, Pig, and Calf Brain Membranes. Naunyn-Schmiedeberg's Arch. Pharmacol. 337: 595-601 (1988) with modifications.

iv) Assay for $5HT_{2A}$

Materials and Methods:

Receptor source : Human Cortex

Radioligand : [^{3}H] Ketanserin (60-90 Ci/mmol)

Final ligand concentration - [2.0 nM]

Non-speeific determinant : Ketanserin - [3.0 μM]

Reference compound : Ketanserin

Positive control : Ketanserin

Incubation conditions :

Reactions are carried out in 50 mM TRIS-HCl (pH 7.5) at room temperature for 90 minutes. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound with the $5HT_{2A}$ binding site.

Literature Reference:

- Leysen J. E., Niemegeers C. J., Van Nueten J. M. and Laduron P. M. [^{3}H]Ketanserin: A Selective Tritiated Ligand for Serotonin$_2$ Receptor Binding Sites. Mol. Pharmacol. 21: 301-314 (1982) with modifications.
- Martin, G. R. and Humphrey, P. P. A. Classification Review: Receptors for 5-HT: Current Perspectives on Classification and Nomenclature. Neuropharmacol. 33(3/4): 261-273 (1994).

Assay for $5HT_{2C}$

Materials and Methods:

Receptor source : Pig choroid plexus membranes

Radioligand : [^{3}H] Mesulergine (50-60 Ci/mmol)

Final ligand concentration - [1.0 nM]

Non-specific determinant : Serotonin - [100 μM]

Reference compound : Mianserin

Positive control : Mianserin

Incubation conditions :

Reactions are carried out in 50 mM TRIS-HCl (pH 7.7) containing 4 mM $CaCl_2$ and 0.1% ascorbic acid at 37 °C for 60 minutes. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound with the $5HT_{2C}$ binding site.

Literature Reference:

- A. Pazos, D. Hoyer, and J. Palacios. The Binding of Serotonergic Ligands to the Porcine Choroid Plexus: Characterization of a New Type of Serotonin Recognition Site. Eur. Jrnl. Pharmacol. 106: 539-546 (1985) with modifications.
- Hoyer, D., Engel, G., et al. Molecular Pharmacology of $5HT_1$ and $5\text{-}HT_2$ Recognition Sites in Rat and Pig Brain Membranes: Radioligand Binding Studies with [3H]-5HT, [3H]-8-OH-DPAT, [^{125}I]-Iodocyanopindolol, [3H]-Mesulergine and [3H]-Ketanserin. Eur. Jrnl. Pharmacol. 118: 13-23 (1985) with modifications.

v) Assay for $5HT_3$

Materials and Methods:

Receptor source : N1E-115 cells

Radioligand :[^{3}H]-GR 65630 (30-70 Ci/mmol)

Final ligand concentration - [0.35 nM]

Non-specific determinant : MDL-72222 - [1.0 µM]

Reference compound : MDL-72222

Positive control : MDL-72222

Incubation conditions :

Reactions are carried out in 20 mM HEPES (pH 7.4) containing 150 mM NaCl at 25 °C for 60 minutes. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound with the $5HT_3$ binding site.

Literature Reference:

- Lummis S. C. R., Kilpatrick G. J. Characterization of $5HT_3$ Receptors in Intact N1E-115 Neuroblastoma Cells. Eur. Jrnl. Pharmacol. 189: 223-227 (1990) with modifications.

• Hoyer D. and Neijt H. C. Identification of Serotonin 5-HT_3 Recognition Sites in Membranes of N1E-115 Neuroblastoma Cells by Radioligand Binding. Mol. Pharmacol. 33: 303 (1988).

• Tyers M. B. 5-HT_3 Receptors and the Therapeutic Potential of $5HT_3$ Receptor Antagonists. Therapie. 46:431-435 (1991).

vi) Assay for $5HT_4$

Materials and Methods:

Receptor source : Guinea pig striatal membranes

Radioligand : [^{3}H] GR-113808 (30-70 Ci/mmol)

Final ligand concentration - [0.2 nM]

Non-specific determinant : Serotonin (5-HT) - [30 µM]

Reference compound : Serotonin (5-HT)

Positive control : Serotonin (5-HT)

Incubation conditions :

Reactions are carried out in 50 mM HEPES (pH 7.4) at 370C for 60 minutes. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound with the $5HT_4$ binding site.

Literature Reference:

• Grossman Kilpatrick, C., et al. Development of a Radioligand Binding Assay for $5HT_4$ Receptors in Guinea Pig and Rat Brain. Brit. J Pharmco. 109: 618-624 (1993).

vii) Assay for $5HT_{5A}$

Materials and Methods:

Receptor source : Human recombinant expressed in HEK 293 cells

Radioligand : [^{3}H] LSD (60-87 Ci/mmol)

Final ligand concentration - [1.0 nM]

Non-specific determinant : Methiothepin mesylate - [1.0 µM]

Reference compound : Methiothepin mesylate

Positive control : Methiothepin mesylate

Incubation conditions :

Reactions are carried out in 50 mM TRIS-HCl (pH 7.4) containing 10 mM $MgSO_4$ and 0.5 mM EDTA at 37 °C for 60 minutes. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and

compared to control values in order to ascertain any interactions of test compound with the cloned $5HT_{5A}$ binding site.

Literature Reference:

- Rees S., et al. FEBS Letters, 355: 242-246 (1994) with modifications

viii) Assay for $5HT_6$

Materials and Methods:

Receptor source : Human recombinant expressed in HEK293 cells

Radioligand : [^{3}H]LSD (60-80 Ci/mmol)

Final ligand concentration - [1.5 nM]

Non-specific determinant : Methiothepin mesylate - [0.1 µM]

Reference compound : Methiothepin mesylate

Positive control : Methiothepin mesylate

Incubation conditions :

Reactions are carried out in 50 mM TRIS-HCl (pH 7.4) containing 10 mM $MgCl_2$, 0.5 mM EDTA for 60 minutes at 37 °C. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound(s) with the cloned serotonin - $5HT_6$ binding site.

Literature Reference:

- Monsma F. J. Jr., et al., Molecular Cloning and Expression of Novel Serotonin Receptor with High Affinity for Tricyclic Psychotropic Drugs. Mol. Pharmacol. (43): 320-327 (1993).

ix) Assay for $5\text{-}HT_7$

Materials and Methods:

Receptor source : Human recombinant expressed in CHO cells

Radioligand : [^{3}H]LSD (60-80 Ci/mmol)

Final ligand concentration - [2.5 nM]

Non-specific determinant : 5-Carboxamidotryptamine (5-CT) - [0.1 µM]

Reference compound : 5-Carboxamidotryptamine

Positive control : 5-Carboxamidotryptamine

Incubation conditions :

Reactions are carried out in 50 mM TRIS-HCl (pH 7.4) containing 10 mM $MgCl_2$, 0.5 mM EDTA for 60 minutes at 37 °C. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control

values in order to ascertain any interactions of test compound(s) with the cloned serotonin - $5HT_7$ binding site.

Literature Reference:

• Y. Shen, E. Monsma, M. Metcalf, P. Jose, M Hamblin, D. Sibley, Molecular Cloning and Expression of a 5-hydroxytryptamine7 Serotonin Receptor Subtype. J. Biol. Chem. 268: 18200-18204.

The following description illustrates the method of preparation of variously substituted compounds of general formula (I), according to the methods described herein. These are provided by the way of illustration only and therefore should not be construed to limit the scope of the invention.

Commercial reagents were utilized without further purification. Room temperature refers to 25 - 30 °C. Melting points are uncorrected. IR spectra were taken using KBr and in solid state. Unless otherwise stated, all mass spectra were carried out using ESI conditions. 1H NMR spectra were recorded at 300 MHz on a Bruker instrument. Deuterated chloroform (99.8 % D) was used as solvent. TMS was used as internal reference standard. Chemical shift values are expressed in are reported in parts per million (δ)-values. The following abbreviations are used for the multiplicity for the NMR signals: s=singlet, bs=broad singlet, d=doublet, t=triplet, q=quartet, qui=quintet, h=heptet, dd=double doublet, dt=double triplet, tt=triplet of triplets, m=multiplet. NMR, mass were corrected for background peaks. Specific rotations were measured at room temperature using the sodium D (589 nm). Chromatography refers to column chromatography performed using 60 – 120 mesh silica gel and executed under nitrogen pressure (flash chromatography) conditions.

Description 1 : N,N-Dimethyl-1-(2'-bromophenylsulfonyl)tryptamine (D1)

A suspension of potassium hydride (9.0 mmoles, 1.2 g. (30 % suspension in mineral oil), washed with THF before use), in THF was stirred and cooled at 0 – 5 °C. To this cooled solution was added a solution of N,N-dimethyltryptamine (6.0 mmoles), in THF, slowly, over 15 min., maintaining the temperature below 10 °C. After completion of addtition, the mixture was warmed to 25 – 30 °C. and maintained for 30 – 45 min. The reaction mixture was then cooled to 0 – 5 °C and solution of 2-bromobenzenesulfonyl chloride in THF (6.0 mmoles, 1.7 g. in 7 mL of THF) was then added to the above well stirred mixture, maintaining the reaction temperature below 10 °C (Exothermic reaction). The reaction mixture was maintained at 20 - 25 °C for further 2 - 4 hrs. After completion of reaction (TLC), the excess of THF was distilled off and the concentrate was diluted with ice-water and extracted with ethyl acetate. Combined ethyl acetate layer was washed with water, dried over sodium sulfate and evaporated under reduced pressure, below 50 °C.

The crude residue was purified by silica gel column chromatography using 30 % methanol in ethyl acetate as a mobile phase, to obtain the intermediate, N,N-Dimethyl-1-(2'-bromophenylsulfonyl)tryptamine, which was identified by IR, NMR and mass spectral analyses.

Description 2 – 55 (D2 – D55) :

Various indole intermediates were subjected to aryl sulfonylation using substituted 2-bromobenzenesulfonyl chloride according to the procedure described in the description 1. These compounds were identified by IR, NMR and mass spectral analyses. The following list includes list of such compounds.

List – 1

	Description	Mass ion $(M+H)^+$
D 1	2-[1-(2-Bromophenylsulfonyl)indol3-yl]ethyl-N,N-dimethylamine	407
D 2	2-[1-(2-Bromophenylsulfonyl)-5-bromoindol3-yl]ethyl-N,N-dimethylamine	485
D 3	2-[1-(2-Bromophenylsulfonyl)-5-chloroindol3-yl]ethyl-N,N-dimethylamine	441
D 4	2-[1-(2-Bromophenylsulfonyl)-5-fluoroindol3-yl]ethyl-N,N-dimethylamine	425
D 5	2-[1-(2-Bromophenylsulfonyl)-5-methylindol3-yl]ethyl-N,N-dimethylamine	421
D 6	2-[1-(2-Bromophenylsulfonyl)-5-methoxyindol3-yl]ethyl-N,N-dimethylamine	437
D 7	2-[1-(2-Bromo-4-methoxyphenylsulfonyl)indol3-yl]ethyl-N,N-dimethylamine	437
D 8	2-[1-(2-Bromo-4-methoxyphenylsulfonyl)-5-bromoindol3-yl]ethyl-N,N-dimethylamine	515
D 9	2-[1-(2-Bromo-4-methoxyphenylsulfonyl)-5-chloroindol3-yl]ethyl-N,N-dimethylamine	471
D 10	2-[1-(2-Bromo-4-methoxyphenylsulfonyl)-5-fluoroindol3-yl]ethyl-N,N-dimethylamine	455
D 11	2-[1-(2-Bromo-4-methoxyphenylsulfonyl)-5-methylindol3-yl]ethyl-N,N-dimethylamine	451
D 12	2-[1-(2-Bromo-4-methoxyphenylsulfonyl)-5-methoxyindol3-yl]ethyl-N,N-dimethylamine	467
D 13	2-[1-(2-Bromophenylsulfonyl)-7-ethylindol3-yl]ethyl-N,N-dimethylamine	435
D 14	2-[1-(2-Bromophenylsulfonyl)-7-chloroindol3-yl]ethyl-N,N-dimethylamine	441
D 15	2-[1-(2-Bromophenylsulfonyl)-5,7-dichloroindol3-yl]ethyl-N,N-dimethylamine	475
D 16	2-[1-(2-Bromophenylsulfonyl)-6,7-dichloroindol3-yl]ethyl-N,N-dimethylamine	475

D 17	2-[1-(2-Bromophenylsulfonyl)-4-chloro-7-methylindol3-yl]ethyl-N,N-dimethylamine	455
D 18	2-[1-(2-Bromophenylsulfonyl)-4-chloro-7-methoxyindol3-yl]ethyl-N,N-dimethylamine	471
D 19	2-[1-(2-Bromophenylsulfonyl)-4,6,7-trichloro-indol3-yl]ethyl-N,N-dimethylamine	509
D 20	2-[1-(2-Bromophenylsulfonyl)-5,7-difluoroindol3-yl]ethyl-N,N-dimethylamine	443
D 21	2-[1-(2-Bromo-4-methylphenylsulfonyl)-5,7-difluoroindol3-yl]ethyl-N,N-dimethylamine	457
D 22	2-[1-(2-Bromo-4-methylphenylsulfonyl)-5-fluoroindol3-yl]ethyl-N,N-dimethylamine	439
D 23	2-[1-(2-Bromophenylsulfonyl)-7-methoxyindol3-yl]ethyl-N,N-dimethylamine	421
D 24	2-[1-(2-Bromo-4-methoxyphenylsulfonyl)-7-methoxyindol3-yl]ethyl-N,N-dimethylamine	467
D 25	2-[1-(2-Bromo-4-methylphenylsulfonyl)indol3-yl]ethyl-N,N-dimethylamine	421
D 26	1-[1-(2-Bromobenzenesulfonyl)-5-bromo-1H-indol-3-yl]-3-dimethylamino-propan-1-ol	515
D 27	1-[1-(2-Bromo-4-methoxybenzenesulfonyl)-1H-indol-3-yl]-3-dimethylamino-propan-1-ol	467
D 28	1-[1-(2-Bromo-4-methylbenzenesulfonyl)-1H-indol-3-yl]-3-dimethylamino-propan-1-ol	451
D 29	1-[1-(2-Bromo-4-methoxybenzenesulfonyl)-5-bromo-1H-indol-3-yl]-3-dimethylamino-propan-1-ol	545
D 30	1-(2-Bromobenzenesulfonyl)-3-[2-(4-methyl-piperazin-1-yl)ethyl]-1H-indole	462
D 31	1-(2-Bromobenzenesulfonyl)-3-[2-(morpholin-1-yl)ethyl]-1H-indole	449
D 32	1-(2-Bromobenzenesulfonyl)-3-[2-(pyrrolidin-1-yl)ethyl]-1H-indole	433
D 33	1-(2-Bromobenzenesulfonyl)-3-[2-(piperidin-1-yl)ethyl]-1H-indole	447
D 34	1-(2-Bromobenzenesulfonyl)-5-bromo-3-[2-(4-methyl-piperazin-1-yl)ethyl]-1H-indole	540
D 35	1-(2-Bromobenzenesulfonyl)-5-bromo-3-[2-(morpholin-1-yl)ethyl]-1H-indole	527

D 36	1-(2-Bromobenzenesulfonyl)-5-bromo-3-[2-(pyrrolidin-1-yl)ethyl]-1H-indole	511
D 37	1-[1-(2-Bromobenzenesulfonyl)-1H-indol-3-yl]-3-(piperidin-1-yl)-propan-1-ol	477
D 38	1-[1-(2-Bromo-4-methoxybenzenesulfonyl)-1H-indol-3-yl]-3-(piperidin-1-yl)-propan-1-ol	507
D 39	1-[1-(2-Bromobenzenesulfonyl)-5-bromo-1H-indol-3-yl]-3-(piperidin-1-yl)-propan-1-ol	555
D 40	1-[1-(2-Bromo-4-methoxybenzenesulfonyl)-5-bromo-1H-indol-3-yl]-3-(piperidin-1-yl)-propan-1-ol	587
D 41	1-[1-(2-Bromobenzenesulfonyl)-1H-indol-3-yl]-3-(pyrrolidin-1-yl)-propan-1-ol	463
D 42	1-[1-(2-Bromo-4-methoxybenzenesulfonyl)-1H-indol-3-yl]-3-(pyrrolidin-1-yl)-propan-1-ol	493
D 43	{2-[1-(2-Bromobenzenesulfonyl)-1H-indol-3-yl]-1-methylethyl}-N,N-dimethylamine	421
D 44	1-[1-(2-Bromo-benzenesulfonyl)-1H-indol-3-yl]-2-dimethylamino-propan-1-ol	437

Description 45: 2-(Benzo[d]isothiazolo[3,2-a]-1H-indol-3-yl-S,S-dioxide)ethylamine (D45)

2-[1-(2-Bromobenzenesulfonyl)-1H-indol-3-yl]ethylamine (0.286 mmoles) was taken in a 100 mL 3 necked round bottomed flask, along with N,N-dimethyl acetamide (40 mL), potassium acetate (0.343 mmoles, 0.337 g.) and dichloro bis(tri-o-tolylphosphine)palladium (0.0143 mmoles, 0.0112 g.). The reaction mixture was maintained under nitrogen atmosphere and was heated to 140 to 160 °C with stirring for 2 to 5 hrs. After the completion of reaction (TLC), the reaction mass is filtered over hyflow, washed with ethyl acetate, and the combined filtrate was diluted with cold water. The aqueous layer was extracted with ethyl acetate (3 X 50 mL). Combined ethyl acetate layer was washed with brine, dried over sodium sulfate and evaporated under reduced pressure, below 50 °C.

The residue obtained was purified by silica gel column chromatography using 20 % methanol in ethyl acetate as an eluent, to afford the title compound, which was identified by IR, NMR and mass spectral analyses.

Mass (m/z) : 299 $(M+H)^+$

Example - 1 : **6-(2-N,N-Dimethylaminoethyl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

1-(2'-bromophenylsulfonyl)-N,N-dimethyltryptamine (0.286 moles) was taken in a 100 mL 3 necked round bottomed flask, along with N,N-dimethyl acetamide (40 mL), potassium acetate (0.286 moles, 0.281 g.) and dichloro bis(tri-o-tolylphosphine)palladium (0.0143 moles, 0.0126 g.). The reaction mixture was maintained under nitrogen atmosphere and was heated to 160 °C with stirring for 16 hrs. After the completion of reaction (TLC), excess of dimethyl acetamide was distilled off under reduced pressure.

The residue obtained was purified by silica gel column chromatography using 20 % methanol in ethyl acetate as an eluent, to afford the title compound, which was identified by IR, NMR and mass spectral analyses. The final desired compound of general formula (I) can be further purified by preparation of their acid addition salts. Melting range (°C) : 128 -131; IR spectra (cm^{-1}) : 2946, 1601, 1461, 1443; Mass (m/z) : 327 $(M+H)^+$; ^{1}H-NMR (δ, ppm) : 2.39 (6H, s), 2.58 - 2.66 (2H, m), 3.11 - 3.19 (2H, m), 7.22 - 7.86 (8H, m).

Example - 2 : **4-Bromo-6-(2-N,N-dimethylaminoethyl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 162 – 165; IR spectra (cm^{-1}) : 2969, 2770, 1344, 1176; Mass (m/z) : 405 $(M+H)^+$, 407 $(M+3)^+$; ^{1}H-NMR (δ ppm) : 2.40 (6H, s), 2.58 - 2.66 (2H, m), 3.08 - 3.16 (2H, m), 7.46 - 7.89 (7H, m).

Example - 3 : **4-Chloro-6-(2-N,N-dimethylaminoethyl)-benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 156 – 158; IR spectra (cm^{-1}) : 2941, 2768, 1440, 1344; Mass (m/z) : 361 $(M+H)^+$; ^{1}H-NMR (δ ppm) : 2.51 (6H, s), 2.72 - 2.80 (2H, m), 3.16 - 3.25 (2H, m), 7.32 - 7.95 (7H, m).

Example - 4 : **6-(2-N,N-Dimethylaminoethyl)-4-fluorobenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 136 – 140; IR spectra (cm^{-1}) : 2966, 1463, 1327; Mass (m/z) : 345 $(M+H)^+$; ^{1}H-NMR (δ ppm) : 2.38 (6H, s), 2.55 - 2.64 (2H, s), 3.05 - 3.14 (2H, m), 7.06 - 7.86 (7H, m).

Example - 5 : **6-(2-N,N-Dimethylaminoethyl)-4-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 138 – 142; IR spectra (cm^{-1}) : 2941, 1607, 1332, 1177; Mass (m/z) : 341 $(M+H)^+$; ^{1}H-NMR (δ ppm) : 2.40 (6H, s), 2.45 (3H, s), 2.58 - 2.66 (2H, s), 3.08 - 3.16 (2H, m), 7.20 - 7.80 (7H, m).

Example - 6 : **6-(2-N,N-Dimethylaminoethyl)-4-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide hydrochloride salt**

Example no. 5 (19.8 mg) was dissolved in 3 mL ether. To this clear solution a mixture of isopropylalcohol-hydrochloric acid (1 mL) was added. Immediately a white precipitate separates out, which was filtered, washed with ether and dried. Melting range (°C) : >250 (dec).

Example - 7 : **6-(2-N,N-Dimethylaminoethyl)-4-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide maleic acid salt**

Example no. 5 (19.4 mg) was dissolved in 3 mL ether. To this clear solution a solution of maleic acid (7.3 mg, dissolved in 3 mL ether:0.5 mL methanol) was added. Immediately a white precipitate separates out, which was filtered, washed with ether and dried. Melting range (°C) : 192 - 194 (dec).

Example - 8 : **6-(2-N,N-Dimethylaminoethyl)-4-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide D,L-malic acid salt**

Example no. 5 (19.8 mg) was dissolved in 3 mL ether. To this clear solution a solution of D,L- malic acid (8.4 mg, dissolved in 3 mL ether:0.5 mL methanol) was added. Immediately a white precipitate separates out, which was filtered, washed with ether and dried. Melting range (°C) : 202 - 204 (dec).

Example - 9 : **6-(2-N,N-Dimethylaminoethyl)-4-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide oxalate salt**

Example no. 5 (19.7 mg) was dissolved in 3 mL ether. To this clear solution a solution of oxalic acid (8.1 mg, dissolved in 3 mL ether:0.5 mL methanol) was added. Immediately a

white precipitate separates out, which was filtered, washed with ether and dried. Melting range (°C) : 226 - 228 (dec).

Example - 10 : **6-(2-N,N-Dimethylaminoethyl)-4-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide citrate salt**

Example no. 5 (20.2 mg) was dissolved in 3 mL ether. To this clear solution a solution of citric acid (12.0 mg, dissolved in 3 mL ether:0.5 mL methanol) was added. Immediately a white precipitate separates out, which was filtered, washed with ether and dried. Melting range (°C) : 184 - 186 (dec).

Example - 11 : **6-(2-N,N-Dimethylaminoethyl)-4-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 148 – 150; IR spectra (cm^{-1}) : 2936, 1613, 1463, 1327; Mass (m/z) : 357 $(M+H)^+$; ^{1}H-NMR (δ ppm) : 2.39 (6H, s), 2.56 - 2.64 (2H, m), 3.06 - 3.14 (2H, m), 3.86 (3H, s), 6.98 - 7.84 (7H, m).

Example - 12 : **6-(2-N,N-Dimethylaminoethyl)-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 146 – 150; IR spectra (cm^{-1}) : 2933, 1603, 1438, 1325; Mass (m/z) : 357 $(M+H)^+$; ^{1}H-NMR (δ ppm) : 2.40 (6H, s), 2.58 - 2.66 (2H, m), 3.09 - 3.18 (2H, m), 3.94 (3H, s), 6.93 - 7.77 (7H, m).

Example - 13 : **4-Bromo-6-(2-N,N-dimethylaminoethyl)-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) :158-160; IR spectra (cm^{-1}) : 2964, 2759, 1434, 1174; Mass (m/z) : 435 $(M+H)^+$, 437 $(M+3)^+$; ^{1}H-NMR (δ ppm) : 2.40 (6H, s), 2.57 - 2.65 (2H, m), 3.05 - 3.13 (2H, m), 3.94 (3H, s), 6.96 - 7.78 (6H, m).

Example - 14 : **4-Chloro-6-(2-N,N-dimethylaminoethyl)-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide** .

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 172 – 174; IR spectra (cm-1) : 2970, 2762, 1590, 1324; Mass (m/z) : 391 $(M+H)^+$; ^{1}H-NMR (δ □ppm) : 2.39 (6H, s), 2.56 - 2.65 (2H, m), 3.09 - 3.13 (2H, m), 3.94 (3H, s), 6.96 - 7.78 (6H, m).

Example - 15 : **6-(2-N,N-Dimethylaminoethyl)-4-fluoro-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 148 – 156; IR spectra (cm^{-1}) : 2943, 1600, 1472, 1438; Mass (m/z) : 375 $(M+H)^+$; ^{1}H-NMR (δ ppm) : 2.38 (6H, s), 2.56 - 2.64 (2H, m), 3.00 - 3.12 (2H, m), 3.94 (3H, s), 6.95 - 7.77 (6H, m).

Example - 16 : **6-(2-N,N-Dimethylaminoethyl)-4-methyl-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 126 – 130; IR spectra (cm^{-1}) : 2963, 1590, 1324, 1174; Mass (m/z) : 371 $(M+H)^+$; ^{1}H-NMR (δ ppm) : 2.40 (6H, s), 2.46 (3H, s), 2.57 - 2.66 (2H, s), 3.11 - 3.15 (2H, m), 3.94 (3H, s), 6.92 - 7.60 (6H, m).

Example - 17 : **6-(2-N,N-Dimethylaminoethyl)-4,8-dimethoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 160 – 164; IR spectra (cm^{-1}) : 2963, 2760, 1591, 1478, 1321, 1171; Mass (m/z) : 387 $(M+H)^+$; ^{1}H-NMR (δ ppm) : 2.40 (6H, s), 2.57 - 2.65 (2H, m), 3.05 - 3.14 (2H, m), 3.87 (3H, s), 3.93 (3H, s), 6.90 - 7.75 (6H, m).

Example - 18 : **6-(2-N,N-Dimethylaminoethyl)-2-ethylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 319 $(M+H)^+$;

Example - 19 : **2-Chloro-6-(2-N,N-dimethylaminoethyl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 166 – 170; IR spectra (cm-1) : 2966, 2770, 1440, 1345; Mass (m/z) : 361 $(M+H)^+$; ^{1}H-NMR (δ,□ ppm) : 2.38 (6H, s), 2.55 - 2.62 (2H, m), 3.10 - 3.19 (2H, m), 7.16 - 7.89 (7H, m).

Example - 20 : **2,4-Dichloro-6-(2-N,N-dimethylaminoethyl)-benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 112 – 116; IR spectra (cm^{-1}) : 2964, 1614, 1559, 1342; 1179, 823, 796; Mass (m/z) : 395 $(M+H)^+$; ^{1}H-NMR (δ ppm) : 2.42 (6H, s), 2.63 - 2.67 (2H, m), 3.10 - 3.18 (2H, m), 7.34 - 7.89 (6H, m).

Example - 21 : **5-Chloro-6-(2-N,N-dimethylaminoethyl)-2-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 153 – 154; Mass (m/z) : 375 $(M+H)^+$; ^{1}H-NMR (δ□ ppm) : 2.42 (6H, s), 2.65 - 2.73 (2H, m), 2.79 (3H, s), 3.42 - 3.51 (2H, m), 7.02 - 7.93 (6H, m).

Example - 22 : **2,4,5-Trichloro-6-(2-N,N-dimethylaminoethyl)-benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 447 (M+18)+, 449 $(M+18)^+$; ^{1}H-NMR (δ□ ppm) : 2.37 (6H, s), 2.67 - 2.75 (2H, m), 3.09 - 3.17 (2H, m), 7.15 – 8.05 (5H, m).

Example - 23 : **6-(2-N,N-Dimethylaminoethyl)-2,4-difluorobenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 180 – 182; IR spectra (cm^{-1}) : 2963, 2789, 1593, 1347, 1184, 919, 796, 586; Mass (m/z) : 363 $(M+H)^+$; ^{1}H-NMR (δ ppm) : 2.37 (6H, s), 2.54 - 2.63 (2H, s), 3.08 - 3.13 (2H, m), 6.93 - 7.90 (6H, m).

Example - 24 : **6-(2-N,N-dimethylaminoethyl)-4-fluoro-8-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 158 – 160; Mass (m/z) : 359 $(M+H)^+$; ^{1}H-NMR (δ ppm) : 2.41 (6H, s), 2.51 (3H, s), 2.59 - 2.67 (2H, m), 3.05 - 3.16 (2H, m), 7.05 - 7.74 (7H, m).

Example - 25 : **2,4-Difluoro-6-(2-N,N-dimethylaminoethyl)-8-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 182 – 184; Mass (m/z) : 377 $(M+H)^+$; ^{1}H-NMR (δ□ ppm) : 2.42 (6H, s), 2.53 (3H, s), 2.60 - 2.68 (2H, m), 3.09 - 3.17 (2H, m), 6.87 - 7.77 (5H, m).

Example - 26 : **6-(2-N,N-Dimethylaminoethyl)-2-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. IR spectra (cm-1) : 2935, 2781, 1342, 1184; Mass (m/z) : 357 $(M+H)^+$; ^{1}H-NMR (δ □ppm) : 2.38 (6H, s), 2.56 - 2.64 (2H, m), 3.09 - 3.17 (2H, m), 4.08 (3H, s), 6.84 - 7.86 (7H, m).

Example - 27 : **6-(2-N,N-Dimethylaminoethyl)-2,8-dimethoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 387 $(M+H)^+$; ^{1}H-NMR (δ □ppm) : 2.47 (6H, s), 2.68 - 2.77 (2H, m), 3.15 - 3.23 (2H, m), 3.94 (3H, s), 4.07 (3H, s), 6.80 - 7.76 (7H, m).

Example - 28 : **6-(2-N,N-Dimethylaminoethyl)-8-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 156 – 158; Mass (m/z) : 341 $(M+H)^+$; ^{1}H-NMR (δ□ ppm) : 2.40 (6H, s), 2.50 (3H, s), 2.58 - 2.66 (2H, m), 3.11 - 3.19 (2H, m), 7.22 - 7.74 (7H, m).

Example - 29 : **6-(3-N,N-Dimethylamino-1-hydroxyprop-1-yl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 144 – 146; IR spectra (cm^{-1}) : 3307, 2826, 1602, 1331, 1182; Mass (m/z) : 357 $(M+H)^+$.

Example - 30 : **4-Bromo-6-(3-N,N-Dimethylamino-1-hydroxyprop-1-yl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and making non-critical variations, the above derivative was prepared. IR spectra (cm^{-1}) : 3430, 2924, 2854, 1332; Mass (m/z) : 435 $(M+H)^+$, 437 $(M+H)^+$.

Example - 31 : **6-(3-N,N-Dimethylamino-1-hydroxyprop-1-yl)-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and making non-critical variations, the above derivative was prepared. IR spectra (cm^{-1}) : 3405, 2927, 1587, 1447, 1365, 1174; Mass (m/z) : 387 $(M+H)^+$.

Example - 32 : **6-(3-N,N-Dimethylamino-1-hydroxyprop-1-yl)-8-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and making non-critical variations, the above derivative was prepared. Melting range (°C) : 116 – 119; IR spectra (cm^{-1}) : 3307, 3059, 2828, 1601, 1325, 1177; Mass (m/z) : 371 $(M+H)^+$.

Example - 33 : **4-Bromo-6-(3-N,N-dimethylamino-1-hydroxyprop-1-yl)-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 37 and making non-critical variations, the above derivative was prepared. Melting range (°C) : 128 -133 ; Mass (m/z) : 465 $(M+H)^+$, 467 $(M+H)^+$.

Example - 34 : **6-[2-(4-Methylpiperazin-1-yl)ethyl]benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. IR spectra (cm^{-1}) : 2938, 2806, 1652, 1372, 1174; Mass (m/z) : 382 $(M+H)^+$; ^{1}H-NMR (δ ppm) : 2.30 (3H, s), 2.53 – 3.0 (12H, m), 7.00 - 8.00 (8H, m).

Example - 35 : **6-[2-Morpholin-4-ylethyl]benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 155 – 158; IR spectra (cm^{-1}) : 2958, 1604, 1443, 1331, 1177; Mass (m/z) : 369 $(M+H)^+$; ^{1}H-NMR (δ ppm) : 2.58 - 2.63 (4H, m), 2.68 - 2.73 (2H, m), 3.14 - 3.18 (2H, m), 3.75 - 3.79 (4H, m), 7.26 - 7.87 (8H, m).

Example - 36 : **6-(2-Pyrrolidin-1-ylethyl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. IR spectra (cm^{-1}) : 2951, 1604, 1444, 1323, 1180; Mass (m/z) : 353 $(M+H)^+$; ^{1}H-NMR (δ ppm) : 1.85 - 1.87 (4H, bs), 2.64- 2.68 (4H, bs), 2.75 - 2.83 (2H, m), 3.17 - 3.26 (2H, m), 7.30 - 7.80 (8H, m).

Example - 37 : **6-(2-Piperidin-1-yl)ethyl]benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. IR spectra (cm^{-1}) : 2931, 1604, 1442, 1330, 1181; Mass (m/z) : 367 $(M+H)^+$; ^{1}H-NMR (δ ppm) : 1.60 - 1.69 (10H, m), 2.57 - 2.67 (2H, m), 3.16 - 3.20 (2H, m), 7.20 - 7.80 (8H, m).

Example - 38 : **4-Bromo-6-[2-morpholin-4-ylethyl]benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 220 – 224; IR spectra (cm^{-1}) : 2929, 2794, 1438, 1338, 1184, 769, 590; Mass (m/z) : 447 $(M+H)^+$, 449 $(M+3)^+$; ^{1}H-NMR (δ ppm) : 2.57 - 2.62 (4H, m), 2.62 - 2.70 (2H, m), 3.08 - 3.16 (2H, m), 3.74 - 3.78 (4H, m), 7.45 - 7.87 (7H, m).

Example - 39 : **4-Bromo-6-(2-pyrrolidin-1-ylethyl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 140 – 144; IR spectra (cm-1) : 2957, 2792, 1346, 1175, 764, 579; Mass (m/z) : 431 $(M+H)^+$, 433 $(M+3)^+$; ^{1}H-NMR (δ□ ppm) : 1.85 - 1.89 (4H, bs), 2.69- 2.73 (4H, bs), 2.77 - 2.79 (2H, m), 3.13 - 3.21 (2H, m), 7.44 - 7.88 (7H, m).

Example - 40 : **4-Bromo-6-[2-(4-methylpiperazin-1-yl)ethyl]benzo[d] isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 180 – 182; IR spectra (cm-1) : 2962, 2784, 1457, 1333, 1175, 797, 590; Mass (m/z) : 460 $(M+H)^+$, 462 $(M+3)^+$; ^{1}H-NMR (δ□ ppm) : 2.32 - 2.38 (3H, s), 2.43 - 2.73 (10H, m), 3.07 - 3.18 (3H, m), 7.44 - 7.87 (7H, m).

Example - 41 : **6-(3-(Piperidin-1-yl)-1-hydroxyprop-1-yl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. IR spectra (cm-1) : 3175, 2939, 1598, 1343, 1177; Mass (m/z) : 397 $(M+H)^+$.

Example - 42 : **6-(3-(Piperidin-1-yl)-1-hydroxyprop-1-yl)-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 177 – 180; Mass (m/z) : 427 $(M+H)^+$.

Example - 43 : **4-Bromo-6-(3-(piperidin-1-yl)-1-hydroxyprop-1-yl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. IR spectra (cm-1) : 2932, 1593, 1338, 1181, 800, 728; Mass (m/z) : 475 $(M+H)^+$.

Example - 44 : **4-Bromo-6-(3-(piperidin-1-yl)-1-hydroxyprop-1-yl)-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 192 – 196; IR spectra (cm-1) : 2927, 1594, 1326, 1172, 798; Mass (m/z) : 507 $(M+H)^+$, 509 $(M+H)^+$.

Example - 45 : **6-(3-(Pyrrolidin-1-yl)-1-hydroxyprop-1-yl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 128 – 130; IR spectra (cm^{-1}) : 3321, 2962, 1598, 1336, 1180; Mass (m/z) : 383 $(M+H)^+$.

Example - 46 : **6-(3-(Pyrrolidin-1-yl)-1-hydroxyprop-1-yl)-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. IR spectra (cm^{-1}) : 3306, 2965, 1602, 1374, 1177; Mass (m/z) : 413 $(M+H)^+$.

Example - 47 : **6-(2-(N,N-Diethylamino)-2-methylethyl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide**

Mass (m/z) : 369 $(M+H)^+$.

Example - 48 : **6-(2-(N,N-Dimethylamino-1-hydroxy-1-yl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide.**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 343 $(M+H)^+$.

Example - 49 : **4-Bromo-6-(2-(N,N-Dimethylamino-1-hydroxy-1-yl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide.**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 148 – 152; (m/z) : 421 $(M+H)^+$, 423 $(M+H)^+$.

Example - 50 : **6-(2-(N,N-Dimethylaminoethyl)-2,4-difluoro-8-Methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide.**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 140 – 142; IR spectra (cm^{-1}) : 2937, 1602, 1332, 1177, 795, 587; Mass (m/z) : 393 $(M+H)^+$; ^{1}H-NMR (δ ppm) : 2.43 (6H, s), 2.62 - 2.70 (2H, m), 3.09 - 3.17 (2H, m), 3.96 (3H, s), 6.87 - 7.80 (5H, m).

Example - 51 : **6-(2-(N,N-Dimethylamino-2-methylethyl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide.**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 341 $(M+H)^+$.

Example - 52 : **6-(2-(N,N-Dimethylaminoethyl)-4-chloro-8-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide.**

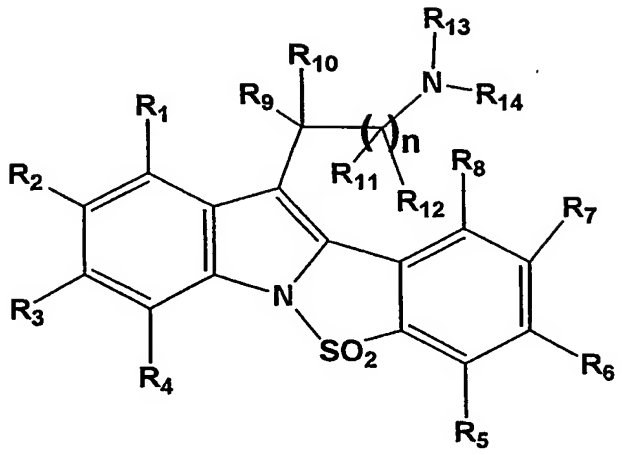
Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : above 250; Mass (m/z) : 375 $(M+H)^+$; ^{1}H-NMR (δ ppm) : 2.63 (3H, s), 2.90 (6H, s), 3.24 (2H, m), 3.61 (2H, m), 7.32 – 7.74 (6H, m).

Example - 53 : **8-(2-(N,N-Dimethylaminoethyl)benzo[d]isothiazolo[3,2-a]benzo(g)indol-S,S-dioxide.**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 377 $(M+H)^+$;

We Claim,

1. A compound of the general formula (I),



General Formula (I)

its derivatives, its analogs, its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts and solvates,

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups such as linear or branched $(C_1\text{-}C_{12})$alkyl, $(C_2\text{-}C_{12})$alkenyl, $(C_2\text{-}C_{12})$alkynyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$cycloalkenyl, bicycloalkyl, bicycloalkenyl, $(C_1\text{-}C_{12})$alkoxy, cyclo$(C_3\text{-}C_7)$alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclylalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocyclylalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together with carbon atoms to which they are attached may form a 5, 6, or 7 membered ring, which may further optionally contain one or more double bonds and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and combinations of double bond and heteroatoms; or R_9 and R_{10} or R_{11} and R_{12} together represent double bond attached to "Oxygen" or "Sulfur"; or R_9 and R_{10} or R_{11} and R_{12}

together with the carbon atoms to which they are attached may form a 3, 4, 5, or 6 membered ring, which may further optionally contain one or more double bonds, and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and also includes combination of one or more double bonds with "heteroatoms", as above defined;

R_{13} and R_{14} may be same or different and each independently represents hydrogen, substituted or unsubstituted groups such as linear or branched $(C_1\text{-}C_{12})$alkyl, $(C_2\text{-}C_{12})$alkenyl, $(C_2\text{-}C_{12})$alkynyl, $(C_2\text{-}C_{12})$alkanoyl $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$cycloalkenyl, bicycloalkyl, bicycloalkenyl, aryl, aralkyl, heteroaryl, heterocyclylalkyl; optionally R_{13} and R_{14} along with the nitrogen atom, may form a 3, 4, 5, 6 or 7–membered heterocyclic ring, wherein the ring may be further substituted, and it may have either one, two or three double bonds or "additional heteroatoms", as defined above; and

"n" is an integer ranging from 1 to 8, preferably 1 to 4, and represents may be either linear or branched carbon chain.

2. A compound according to Claim -1, which is selected from the group consisting of:
6-(2-N,N-Dimethylaminoethyl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
4-Bromo-6-(2-N,N-dimethylaminoethyl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
4-Chloro-6-(2-N,N-dimethylaminoethyl)-benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-N,N-Dimethylaminoethyl)-4-fluorobenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-N,N-Dimethylaminoethyl)-4-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-N,N-Dimethylaminoethyl)-4-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide hydrochloride salt;
6-(2-N,N-Dimethylaminoethyl)-4-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide maleate salt;
6-(2-N,N-Dimethylaminoethyl)-4-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide D,L-malic acid salt;
6-(2-N,N-Dimethylaminoethyl)-4-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide oxalate salt;
6-(2-N,N-Dimethylaminoethyl)-4-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide citrate salt;
6-(2-N,N-Dimethylaminoethyl)-4-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-N,N-Dimethylaminoethyl)-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
4-Bromo-6-(2-N,N-dimethylaminoethyl)-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

4-Chloro-6-(2-N,N-dimethylaminoethyl)-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

6-(2-N,N-Dimethylaminoethyl)-4-fluoro-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

6-(2-N,N-Dimethylaminoethyl)-4-methyl-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

6-(2-N,N-Dimethylaminoethyl)-4,8-dimethoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

6-(2-N,N-Dimethylaminoethyl)-2-ethylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

2-Chloro-6-(2-N,N-dimethylaminoethyl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

2,4-Dichloro-6-(2-N,N-dimethylaminoethyl)-benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

2,3-Dichloro-6-(2-N,N-dimethylaminoethyl)-benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

5-Chloro-6-(2-N,N-dimethylaminoethyl)-2-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

2,4,5-Trichloro-6-(2-N,N-dimethylaminoethyl)-benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

6-(2-N,N-Dimethylaminoethyl)-2,4-difluorobenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

6-(2-N,N-dimethylaminoethyl)-4-fluoro-8-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

2,4-Difluoro-6-(2-N,N-dimethylaminoethyl)-8-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

6-(2-N,N-Dimethylaminoethyl)-2-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

6-(2-N,N-Dimethylaminoethyl)-2,8-dimethoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

6-(2-N,N-Dimethylaminoethyl)-8-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

6-(3-N,N-Dimethylamino-1-hydroxyprop-1-yl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

4-Bromo-6-(3-N,N-Dimethylamino-1-hydroxyprop-1-yl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

6-(3-N,N-Dimethylamino-1-hydroxyprop-1-yl)-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

6-(3-N,N-Dimethylamino-1-hydroxyprop-1-yl)-8-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

4-Bromo-6-(3-N,N-dimethylamino-1-hydroxyprop-1-yl)-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

6-[2-(4-Methylpiperazin-1-yl)ethyl]benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

6-[2-Morpholin-4-ylethyl]benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

6-(2-Pyrrolidin-1-ylethyl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

6-(2-Piperidin-1-yl)ethyl]benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

4-Bromo-6-[2-morpholin-4-ylethyl]benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

4-Bromo-6-(2-pyrrolidin-1-ylethyl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;

4-Bromo-6-[2-(4-methylpiperazin-1-yl)ethyl]benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(3-(Piperidin-1-yl)-1-hydroxyprop-1-yl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(3-(Piperidin-1-yl)-1-hydroxyprop-1-yl)-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
4-Bromo-6-(3-(piperidin-1-yl)-1-hydroxyprop-1-yl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
4-Bromo-6-(3-(piperidin-1-yl)-1-hydroxyprop-1-yl)-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(3-(Pyrrolidin-1-yl)-1-hydroxyprop-1-yl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(3-(Pyrrolidin-1-yl)-1-hydroxyprop-1-yl)-8-methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-(N,N-Diethylamino)-2-methylethyl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-(N,N-Dimethylamino-1-hydroxy-1-yl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
4-Bromo-6-(2-(N,N-Dimethylamino-1-hydroxy-1-yl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-(N,N-Dimethylaminoethyl)-2,4-difluoro-8-Methoxybenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
6-(2-(N,N-Dimethylamino-2-methylethyl)benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
4-Chloro-6-(2-(N,N-Dimethylaminoethyl)-8-methylbenzo[d]isothiazolo[3,2-a]indol-S,S-dioxide;
8-(2-(N,N-Dimethylaminoethyl)benzo[d]isothiazolo[3,2-a]benzo(g)indol-S,S-dioxide; and
its stereoisomers, its N-oxides, its polymorphs, its pharmaceutically acceptable salts and solvates.

3. A pharmaceutical composition comprising either of a pharmaceutically acceptable carrier, diluent/s, excipient/s or solvates along with a therapeutically effective amount of a compound according to Claim-1, its derivatives, its analogs, its tautomeric forms, its stereoisomers, its geometric forms, its N-oxides, its polymorphs, its pharmaceutically acceptable salts, or solvates.

4. A pharmaceutical composition according to Claim-3, in the form of a tablet, capsule, powder, lozenges, suppositories, syrup, solution, suspension or injectable, administered in, as a single dose or multiple dose units.

5. Use of compound of general formula (I), as defined in Claim-1 or a pharmaceutical composition as defined in Claim-3 for preparing medicaments.

6. Use of compound of general formula (I), as defined in Claim-1 or a pharmaceutical composition as defined in Claim-3 for the treatment where a modulation of 5-HT activity is desired.

7. Use of a compound as claimed in Claim-1 for the manufacture of a medicament for the treatment and/or prevention of clinical conditions for which a selective action on 5-HT receptors is indicated.

8. Use of a compound as claimed in Claim-1 for the treatment and/or prevention of clinical conditions such as anxiety, depression, convulsive disorders, obsessive-compulsive disorders, migraine headache, cognitive memory disorders, ADHD (Attention Deficient Disorder/ Hyperactivity Syndrome), personality disorders, psychosis, paraphrenia, psychotic depression, mania, schizophrenia, schizophreniform disorders, withdrawal from drug abuse, panic attacks, sleep disorders and also disorders associated with spinal trauma and /or head injury.

9. Use of a compound as claimed in Claim-1 for the treatment of mild cognitive impairment and other neurodegenerative disorders like Alzheimer's disease, Parkinsonism and Huntington's chorea.

10. Use of a compound as claimed in Claim-1 for the treatment of certain GI (Gastrointestinal) disorders such as IBS (Irritable bowel syndrome) or chemotherapy induced emesis.

11. Use of a compound as claimed in Claim-1 to reduce morbidity and mortality associated with the excess weight.

12. Use of a radiolabelled compound as claimed in Claim-1, as a diagnostic tool for modulating 5-HT receptor function.

13. Use of a compound as claimed in Claims 1 in combination with a 5-HT re-uptake inhibitor, and / or a pharmaceutically acceptable salt thereof.

14. A compound of the general formula (1), its derivatives, its analogs, its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts and its pharmaceutically acceptable solvates for preparing a medicament.

15. A method for the treatment and/or prophylaxis of clinical conditions such as anxiety, convulsive disorders, obsessive-compulsive disorders, migraine headache, cognitive memory disorders, ADHD (Attention Deficient Disorder/ Hyperactivity Syndrome), personality disorders, psychosis, paraphrenia, psychotic depression, mania, schizophrenia, schizophreniform disorders, withdrawal from drug abuse, panic attacks, sleep disorders and also disorders associated with spinal trauma and /or head injury which comprises administering to a patient in need thereof, an effective amount of a compound of general formula (I) as claimed in Claim-1.

16. A method for the treatment and/or prophylaxis of mild cognitive impairment and other neurodegenerative disorders like Alzheimer's disease, Parkinsonism and Huntington's chorea which comprises administering to a patient in need thereof, an effective amount of a compound of general formula (I) as claimed in Claim-1.

17. A method for the treatment of certain GI (Gastrointestinal) disorders such as IBS (Irritable bowel syndrome) or chemotherapy induced emesis using a compound of general formula (I) as claimed in Claim-1.

18. A method to reduce morbidity and mortality associated with the excess weight using a compound of general formula (I) as claimed in Claim-1.

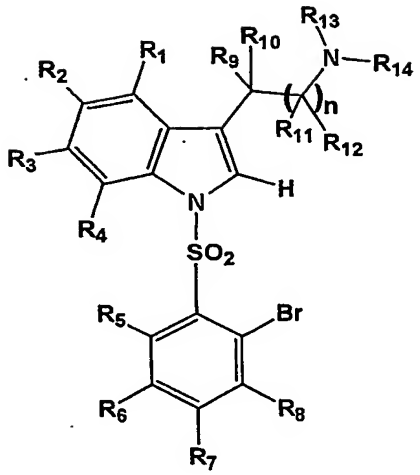
19. A process for the preparation of a compound of general formula (I),-

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups such as linear or branched $(C_1\text{-}C_{12})$alkyl, $(C_2\text{-}C_{12})$alkenyl, $(C_2\text{-}C_{12})$alkynyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$cycloalkenyl, bicycloalkyl, bicycloalkenyl, $(C_1\text{-}C_{12})$alkoxy, cyclo$(C_3\text{-}C_7)$alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclylalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocyclylalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl,

aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together with carbon atoms to which they are attached may form a 5, 6, or 7 membered ring, which may further optionally contain one or more double bonds and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and combinations of double bond and heteroatoms; or R_9 and R_{10} or R_{11} and R_{12} together represent double bond attached to "Oxygen" or "Sulfur"; or R_9 and R_{10} or R_{11} and R_{12} together with the carbon atoms to which they are attached may form a 3, 4, 5, or 6 membered ring, which may further optionally contain one or more double bonds, and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and also includes combination of one or more double bonds with "heteroatoms", as above defined;

R_{13} and R_{14} may be same or different and each independently represents hydrogen, substituted or unsubstituted groups such as linear or branched $(C_1\text{-}C_{12})$alkyl, $(C_2\text{-}C_{12})$alkenyl, $(C_2\text{-}C_{12})$alkynyl, $(C_2\text{-}C_{12})$alkanoyl $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$cycloalkenyl, bicycloalkyl, bicycloalkenyl, aryl, aralkyl, heteroaryl, heterocyclylalkyl; optionally R_{13} and R_{14} along with the nitrogen atom, may form a 3, 4, 5, 6 or 7–membered heterocyclic ring, wherein the ring may be further substituted, and it may have either one, two or three double bonds or "additional heteroatoms", as defined above; and

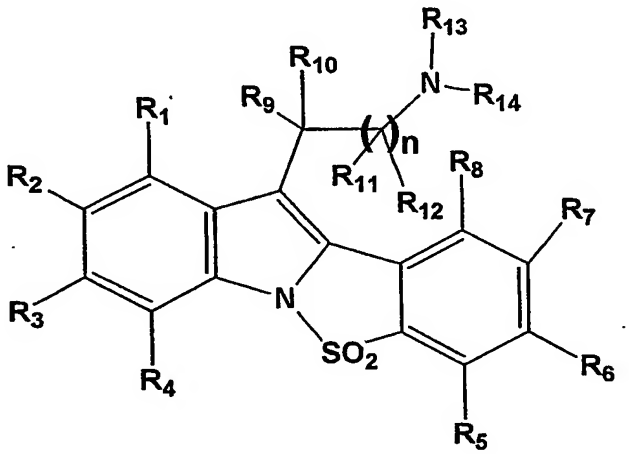
"n" is an integer ranging from 1 to 8, preferably 1 to 4, and represents may be either linear or branched carbon chain; which comprises of cyclizing, a compound of formula (II) given below,



(II)

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14} and "n", wherein all the symbols are as defined above, using a Pd(0) or Pd (II) derivative as a catalyst.

20. A process for the preparation of a compound of general formula (I),



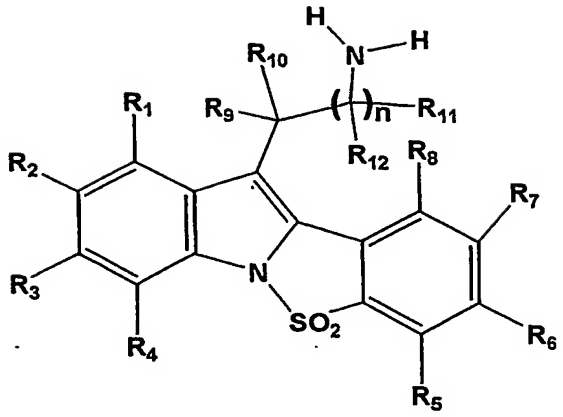
(I)

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups such as linear or branched (C_1-C_{12})alkyl, (C_2-C_{12})alkenyl, (C_2-C_{12})alkynyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkenyl, bicycloalkyl, bicycloalkenyl, (C_1-C_{12})alkoxy, cyclo(C_3-C_7)alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclylalkyloxy, acyl, acyloxy, acylamino, monoalkylamino,

dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocyclylalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together with carbon atoms to which they are attached may form a 5, 6, or 7 membered ring, which may further optionally contain one or more double bonds and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and combinations of double bond and heteroatoms; or R_9 and R_{10} or R_{11} and R_{12} together represent double bond attached to "Oxygen" or "Sulfur"; or R_9 and R_{10} or R_{11} and R_{12} together with the carbon atoms to which they are attached may form a 3, 4, 5, or 6 membered ring, which may further optionally contain one or more double bonds, and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and also includes combination of one or more double bonds with "heteroatoms", as above defined;

R_{13} and R_{14} may be same or different and each independently represents hydrogen, substituted or unsubstituted groups such as linear or branched (C_1-C_{12})alkyl, (C_2-C_{12})alkenyl, (C_2-C_{12})alkynyl, (C_2-C_{12})alkanoyl (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkenyl, bicycloalkyl, bicycloalkenyl, aryl, aralkyl, heteroaryl, heterocyclylalkyl; optionally R_{13} and R_{14} along with the nitrogen atom, may form a 3, 4, 5, 6 or 7–membered heterocyclic ring, wherein the ring may be further substituted, and it may have either one, two or three double bonds or "additional heteroatoms", as defined above; and

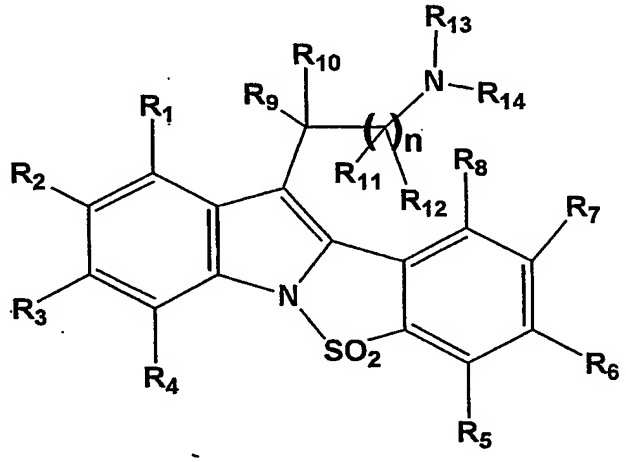
"n" is an integer ranging from 1 to 8, preferably 1 to 4, and represents may be either linear or branched carbon chain; which comprises of reacting a compound **(III)** given below,



(III)

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12} and "n" are as defined above, with a suitable alkylating agent such as $R_{13}X$ or $R_{14}X$ or $XR_{13}R_{14}X$ in successive steps or in one step, wherein X is good leaving group such as halogen and hydroxyl .

21. A process for the preparation of a compound of general formula (I),

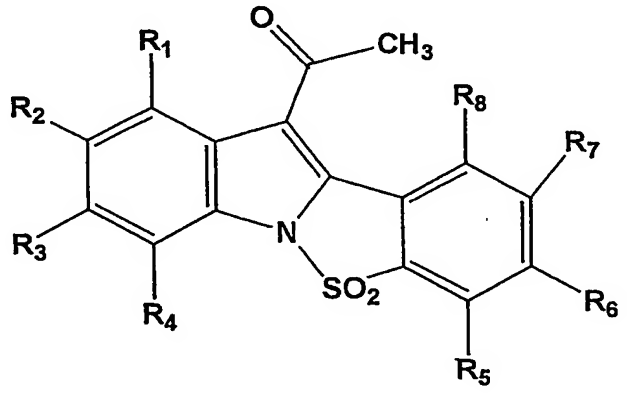


wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups such as linear or branched $(C_1\text{-}C_{12})$alkyl, $(C_2\text{-}C_{12})$alkenyl, $(C_2\text{-}C_{12})$alkynyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$cycloalkenyl, bicycloalkyl, bicycloalkenyl, $(C_1\text{-}C_{12})$alkoxy, cyclo$(C_3\text{-}C_7)$alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclylalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocyclylalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl,

aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together with carbon atoms to which they are attached may form a 5, 6, or 7 membered ring, which may further optionally contain one or more double bonds and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and combinations of double bond and heteroatoms; or R_9 and R_{10} or R_{11} and R_{12} together represent double bond attached to "Oxygen" or "Sulfur"; or R_9 and R_{10} or R_{11} and R_{12} together with the carbon atoms to which they are attached may form a 3, 4, 5, or 6 membered ring, which may further optionally contain one or more double bonds, and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and also includes combination of one or more double bonds with "heteroatoms", as above defined;

R_{13} and R_{14} may be same or different and each independently represents hydrogen, substituted or unsubstituted groups such as linear or branched $(C_1\text{-}C_{12})$alkyl, $(C_2\text{-}C_{12})$alkenyl, $(C_2\text{-}C_{12})$alkynyl, $(C_2\text{-}C_{12})$alkanoyl $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$cycloalkenyl, bicycloalkyl, bicycloalkenyl, aryl, aralkyl, heteroaryl, heterocyclylalkyl; optionally R_{13} and R_{14} along with the nitrogen atom, may form a 3, 4, 5, 6 or 7–membered heterocyclic ring, wherein the ring may be further substituted, and it may have either one, two or three double bonds or "additional heteroatoms", as defined above; and

"n" is an integer ranging from 1 to 8, preferably 1 to 4, and represents may be either linear or branched carbon chain; which comprises of reacting a compound of **(IV)** given below,



(IV)

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7 and R_8 are as defined above, with formaldehyde and a compound of formula (V) given below,

$NHR_{13}R_{14}$

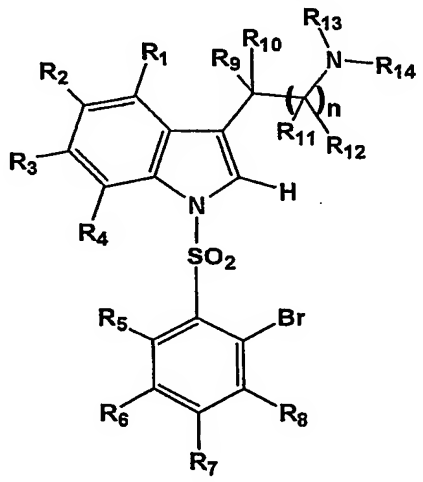
(V)

wherein R_{13} and R_{14} are as defined above.

22. A process for the preparation of compound of formula (I), which comprises of either chemically or catalytically reducing compounds containing =C(O) group/s in the side chain, to the corresponding –C(OH,H) or –C(H,H) compound.

23. A process according to Claim-19 to Claim-22, comprising of carrying out one or more of the following optional steps: i) removing any protecting group; ii) resolving the racemic mixture into pure enantiomers by the known methods and iii) preparing a pharmaceutically acceptable salt of a compound of formula (I) and/or iv preparing a pharmaceutically acceptable prodrug thereof.

24. Novel intermediates defined by general formula **(II)**,



(II)

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups such as linear or branched (C_1-C_{12})alkyl, (C_2-C_{12})alkenyl, (C_2-C_{12})alkynyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkenyl, bicycloalkyl, bicycloalkenyl, (C_1-C_{12})alkoxy, cyclo(C_3-C_7)alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclylalkyloxy, acyl, acyloxy, acylamino, monoalkylamino,

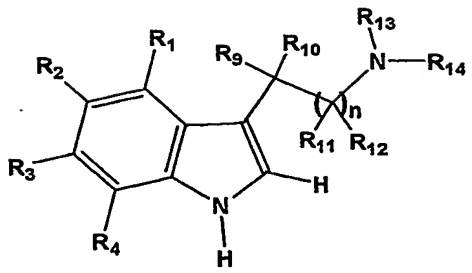
dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocyclylalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together with carbon atoms to which they are attached may form a 5, 6, or 7 membered ring, which may further optionally contain one or more double bonds and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and combinations of double bond and heteroatoms; or R_9 and R_{10} or R_{11} and R_{12} together represent double bond attached to "Oxygen" or "Sulfur"; or R_9 and R_{10} or R_{11} and R_{12} together with the carbon atoms to which they are attached may form a 3, 4, 5, or 6 membered ring, which may further optionally contain one or more double bonds, and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and also includes combination of one or more double bonds with "heteroatoms", as above defined;

R_{13} and R_{14} may be same or different and each independently represents hydrogen, substituted or unsubstituted groups such as linear or branched $(C_1\text{-}C_{12})$alkyl, $(C_2\text{-}C_{12})$alkenyl, $(C_2\text{-}C_{12})$alkynyl, $(C_2\text{-}C_{12})$alkanoyl $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$cycloalkenyl, bicycloalkyl, bicycloalkenyl, aryl, aralkyl, heteroaryl, heterocyclylalkyl; optionally R_{13} and R_{14} along with the nitrogen atom, may form a 3, 4, 5, 6 or 7–membered heterocyclic ring, wherein the ring may be further substituted, and it may have either one, two or three double bonds or "additional heteroatoms", as defined above;

"n" is an integer ranging from 1 to 8, preferably 1 to 4, and represents either linear or branched carbon chain; and its stereoisomers and its salts.

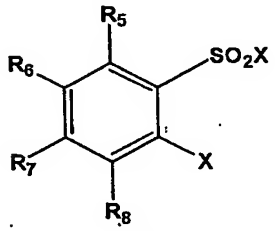
25. A process provided for the preparation of novel intermediate of the general formula (II) according to any one of the routes,

Route - i) reacting a compound of formula (VI) given below,



(VI)

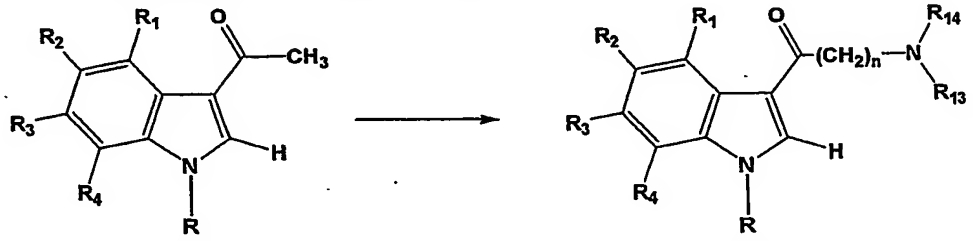
wherein R_1, R_2, R_3, R_4, R_9, R_{10}, R_{11},R_{12}, R_{13} and R_{14} are as defined earlier; with a compound of formula (VII)



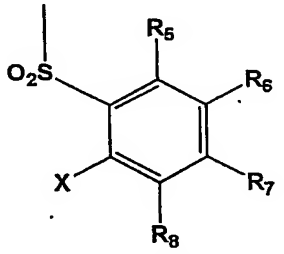
(VII)

wherein R_5, R_6, R_7 and R_8 are as defined earlier and X is a halogen, preferably chloro, bromo or iodo;

Route - ii) according to the following route

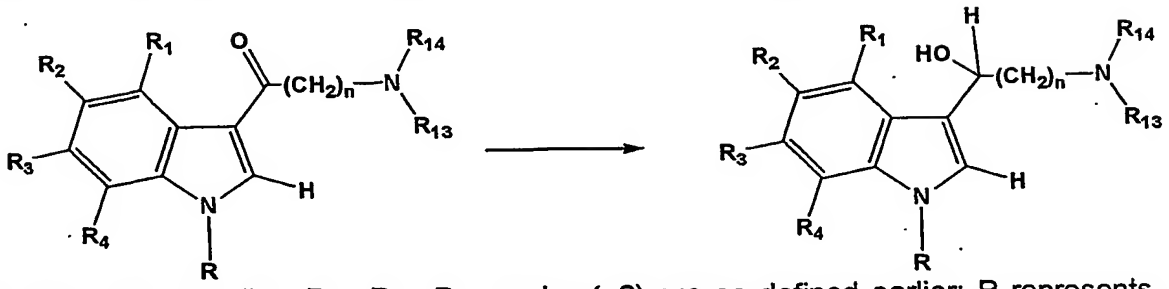


wherein R_1, R_2, R_3, R_4, R_{11}, R_{12}, R_{13}, R_{14} and n (=2) are as defined earlier; R represents either of hydrogen or a group such as,

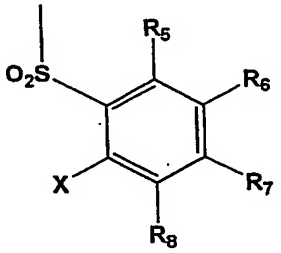


wherein X is halogen such as chloro, bromo or iodo; R_5, R_6, R_7 and R_8 are as defined earlier; in presence of amine hydrochloride and formaldehyde;

Route - iii) reducing another compound of formula (II) as follows,

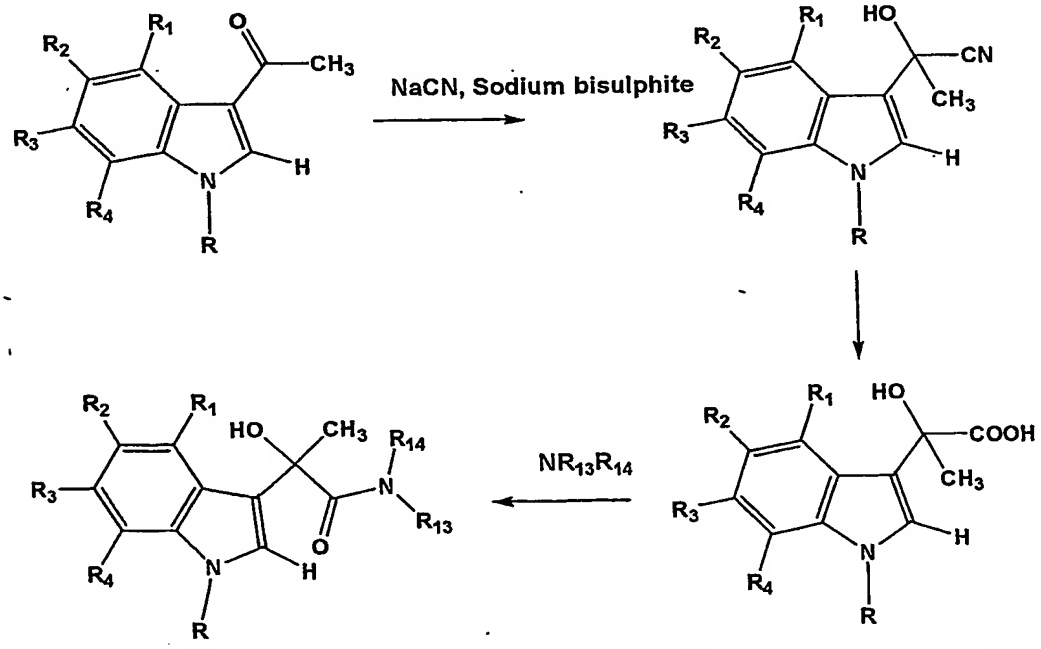


wherein R_1, R_2, R_3, R_4, R_{11}, R_{12}, R_{13}, R_{14} and n (=2) are as defined earlier; R represents either of hydrogen or a group such as,

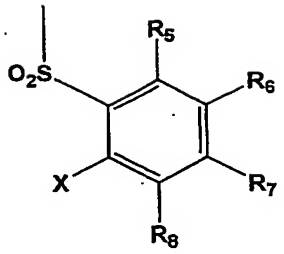


wherein X is halogen such as chloro, bromo or iodo; R_5, R_6, R_7 and R_8 are as defined earlier; by use of known various methods of either catalytic (for example, palladium/carbon), chemical (for example, sodium borohydride) or enzymatic reduction;

Route - iv) according to the following route,

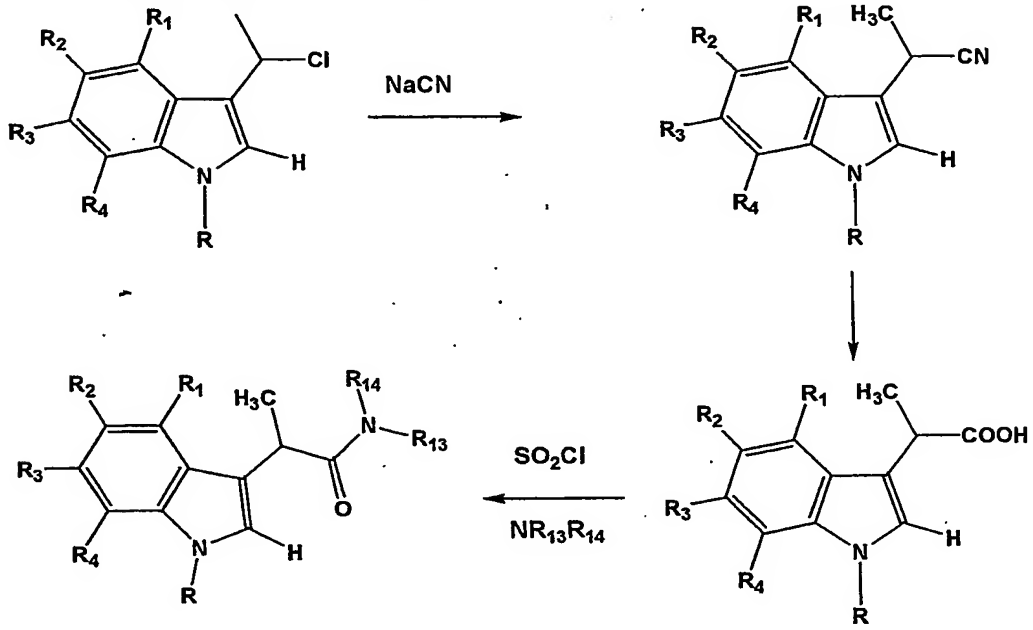


wherein R_1, R_2, R_3, R_4, R_{11}, R_{12}, R_{13}, R_{14} and n are as defined earlier; R represents either of hydrogen or a group such as,

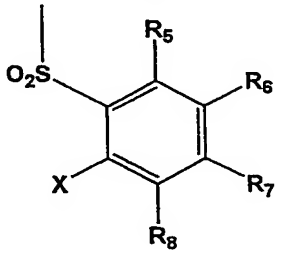


wherein X is halogen such as chloro, bromo or iodo; R_5, R_6, R_7 and R_8 are as defined earlier;

Route - v) according to the following route,

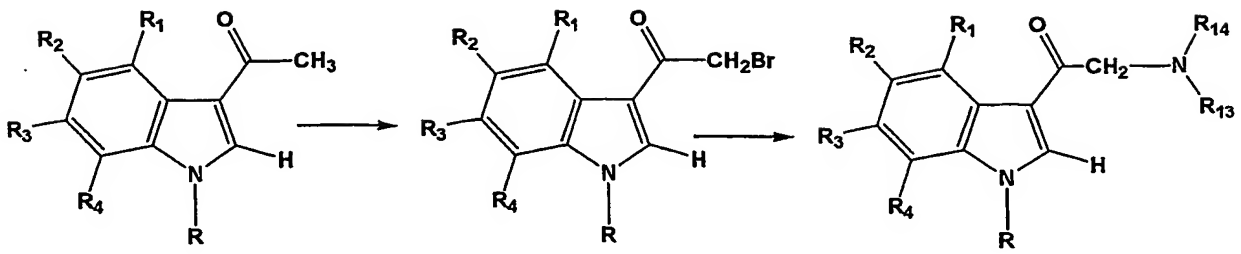


wherein R_1, R_2, R_3, R_4, R_{11}, R_{12}, R_{13}, R_{14} and n are as defined in relation to formula **(I)**; R represents either of hydrogen or a group such as,

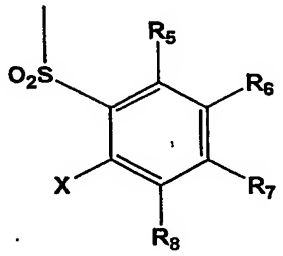


wherein X is halogen such as chloro, bromo or iodo; R_5, R_6, R_7 and R_8 are as defined earlier;

Route - vi) according to the following route,

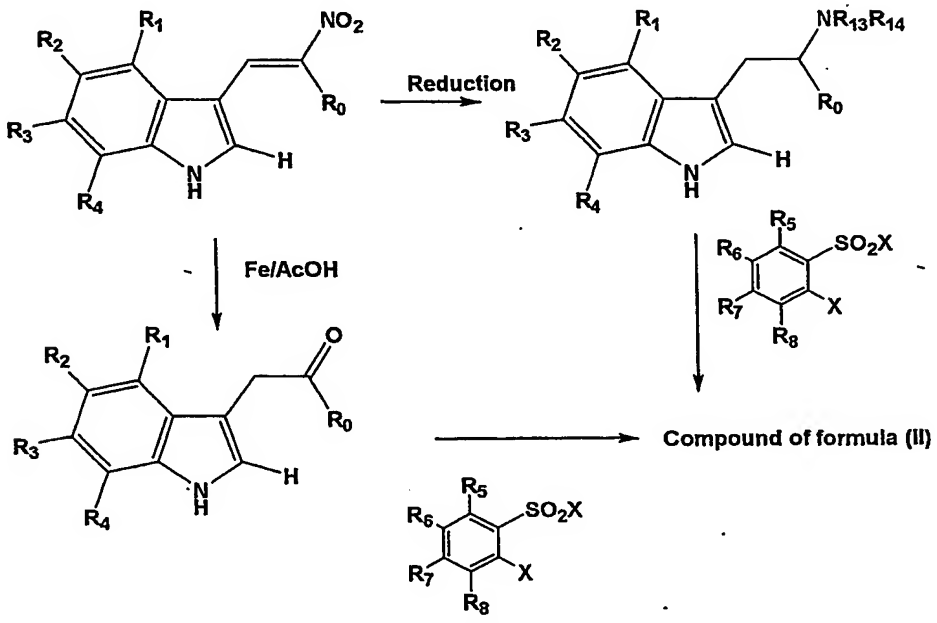


wherein R_1, R_2, R_3, R_4, R_{11}, R_{12}, R_{13}, R_{14} and n are as defined earlier; R represents either of hydrogen or a group such as,



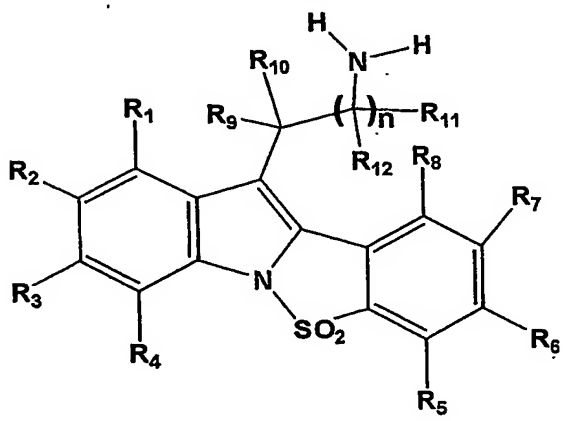
wherein X is halogen such as chloro, bromo or iodo; R_5, R_6, R_7 and R_8 are as defined earlier; and

Route - vii) according to the following route,



wherein R_1, R_2, R_3, R_4, R_{11}, R_{12}, R_{13}, R_{14} and n (=2) are as defined earlier; R_0 is hydrogen or alkyl group.

26. Novel intermediates of general formula **(III)** are represented as given below,



(III)

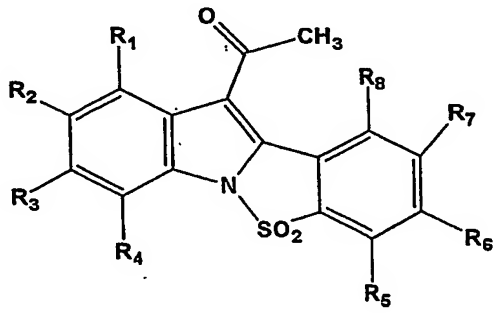
wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups such as linear or branched $(C_1\text{-}C_{12})$alkyl, $(C_2\text{-}C_{12})$alkenyl, $(C_2\text{-}C_{12})$alkynyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$cycloalkenyl, bicycloalkyl, bicycloalkenyl, $(C_1\text{-}C_{12})$alkoxy, cyclo$(C_3\text{-}C_7)$alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclylalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocyclylalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together with carbon atoms to which they are attached may form a 5, 6, or 7 membered ring, which may further optionally contain one or more double bonds and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and combinations of double bond and heteroatoms; or R_9 and R_{10} or R_{11} and R_{12} together represent double bond attached to "Oxygen" or "Sulfur"; or R_9 and R_{10} or R_{11} and R_{12} together with the carbon atoms to which they are attached may form a 3, 4, 5, or 6 membered ring, which may further optionally contain one or more double bonds, and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and

also includes combination of one or more double bonds with "heteroatoms", as above defined.

"n" is an integer ranging from 1 to 8. It is preferred that n be 1 to 4. The carbon chains which "n" represents may be either linear or branched.

27. A process provided for the preparation of novel intermediate of the general formula (III) which comprises of cyclizing a suitable compounds of formula (II).

28. Novel intermediates defined of general formula (IV),

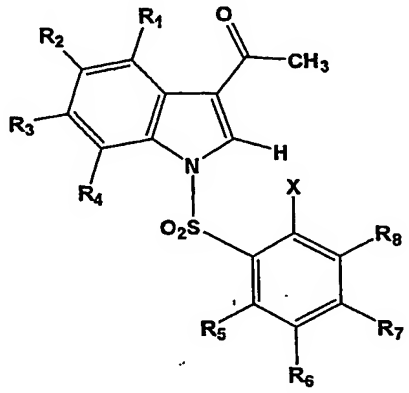


(IV)

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7 and R_8 are as may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups such as linear or branched $(C_1\text{-}C_{12})$alkyl, $(C_2\text{-}C_{12})$alkenyl, $(C_2\text{-}C_{12})$alkynyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$cycloalkenyl, bicycloalkyl, bicycloalkenyl, $(C_1\text{-}C_{12})$alkoxy, cyclo$(C_3\text{-}C_7)$alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclylalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocyclylalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together with carbon atoms to which they are attached may form a 5, 6, or 7 membered ring, which may further optionally contain one or more double bonds and/or one

or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and combinations of double bond and heteroatoms; and R_9 and R_{10} here are represented as double bond attached to "Oxygen".

29. A process provided for the preparation of novel intermediate of the general formula (IV) which comprises of cyclizing compounds of formula (VIII)



wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7 and R_8 are as defined above; using a Pd(0) or Pd (II) derivative as a catalyst.

Dated this the 17th day of June 2003

H. SUBRAMANIAM
Of Subramaniam, Nataraj & Associates
Attorneys for the Applicants

Abstract

The present invention relates to novel tetracyclic arylsulfonyl indoles, their derivatives, their analogues, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates described herein and pharmaceutically acceptable compositions containing them. This invention particularly relates to novel tetracyclic arylsulfonyl indoles of the general formula (I), their derivatives, their analogues, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates described herein and pharmaceutically acceptable compositions containing them. This invention also relates to process/es for preparing such compound/s of general formula (I), composition/s containing effective amount/s of such a compound and the use of such a compound/composition in therapy.